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The Toxicity of Hexachlorobenzene in a Twelve Month Study in Beagle Dogs

Mason Research Inst, Worcester, Mass

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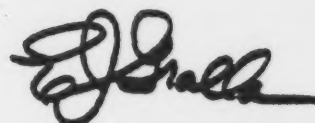
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A 12 Month Report

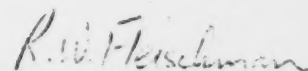
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SUMMARY AND CONCLUSIONS

Hexachlorobenzene (HCB) was administered in gelatin capsules to male and female beagles at 1,000, 100, 10 and 1 mg/dog/day for twelve months. Mortality, anorexia and weight loss occurred primarily at the highest but also to a lesser degree at the next lower level. After approximately three months, body weight stabilized or losses were regained. Clinical laboratory changes found immediately before death in severely affected animals which may have been related to malnutrition, included anemia, hypoglycemia, hypocalcemia and testicular degeneration. A dose related neutrophilia appeared in the two highest dosage groups. The most widespread pathological lesions were confined to the abdomen and included serositis; necrosis, fibrosis and steatitis of the omentum, and lymphoid atrophy at the two highest dose levels. Nodular hyperplasia of gastric lymphoid tissue was found in all treated animals including those at 1 mg/day (6.5-10.0 mg/kg). Four severely affected animals at the highest dose level showed a generalized vasculitis and one had amyloidosis. One dog from each of the two highest levels had bile duct hyperplasia and subchronic pericholangitis. Bile and perirenal fat showed a time and dose related accumulation of HCB.

No hepatic fluorescence was found at necropsy, indicating these dogs were free of porphyria. Nevertheless, hepatic fluorescence was induced in female rats by feeding the material which was used in the canine study. The possible reasons for this species specific effect are discussed.

SUMMARY OF HCB RELATED RESPONSES

Dog Number	1,096	1,115	1,077	1,107	1,128	1,075	1,100	1,089	1,098	1,104	1,109	1,070
Effects: Dose (mg/day)	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
General:												
Mortality or Moribundity	M43	D79	M79	M88	S143	M227	M229	S365	S365	S365	S365	S365
Body Weight Loss (kg)	4.2	3.9	4.5	2.1	1.3	3.5	4.0	1.5	4.1	2.2	+	+
Anemia	+++											
Hypoglycemia	+++		+++	+++								
Hypocalcemia	+		+	+								
Decreased Blood CO ₂	++						+	+	+	+		
Lymphoid Atrophy		++	++	+		+						
Neutrophilia	+++		++		+++	+++	+++	++	+	+		
Polyarteritis	+++					++	+++					
Gastrointestinal:												
Anorexia (% of Days Noted)	85	25	26	24	47	65	21	14	18	36	3	14
Diarrhea (% of Days Noted)	7.5	1.3	11	11	11	8	9	14	3	9	2	6
Ascites (cc)					35	10	3	3				
Serositis			+++	+	++	++						
Omental Adhesions			+				+	+++	+			
Omental Necrosis/Fibrosis			+/++			/++	+/++					+
Lymphoid Hyperplasia (Gastric)					+++				++	+	++	+++
Hepatic:												
Alk. PO ₄ Elevation			+++	+			++++					
T'ases Elevations				+	++							
Bile Duct Hyperplasia							++					
Pericholangitis							++					
Other												
Amyloidosis	+++											
Testicular Degeneration				++		++						
Dog Number	1,114	1,127	1,121	1,076	1,102	1,079	1,082	1,083	1,086	1,091	1,123	1,110
Dose (mg/day)	100	100	100	100	100	100	100	100	100	100	100	100
General: Wgt Loss (kg)												
	2.5	0.1	+	+	2.1	+	2.9	1.0	+	+	+	+
Mortality or Moribundity	M52	S143	S143	S143	D297	S365	S365	S365	S365	S365	S365	S365
Hypoglycemia	+++				+++							
Hypocalcemia					++							
Lymphoid Atrophy	++				+++							
Neutrophilia	++			+++			+++	++			++	+
Gastrointestinal:												
Anorexia %	73	8	15	50	36	12	15	1	2.5	1.4	2.7	4
Diarrhea %	14	2	0.7	6	6	4	3	2	0.3	0.5	0.3	0.3
Omental Adhesions							+++					
Omental Necrosis/Fibrosis					+		++			+		
Lymphoid Hyperplasia (Gastric)		++	++	++		++	++	++	++	+++	++	+++
Hepatic:												
Alk. PO ₄ Elevation	++				++							
T'ases Elevations	++				++							
Bile Duct Hyperplasia					++							
Pericholangitis					++							
Other:												
Testicular Degeneration												
Dog Number	1,117	1,094	1,125	1,080	1,071	1,074	1,078	1,084	1,085	1,097	1,103	1,120
Dose (mg/day)	10	10	10	10	10	10	10	10	10	10	10	10
Lymphoid Hyperplasia	+	+++	+	+	+++	+	++	+	+++		+	++
Dog Number	1,105	1,124	1,119	1,126	1,090	1,092	1,095	1,099	1,101	1,106	1,111	1,116
Dose (mg/day)	1	1	1	1	1	1	1	1	1	1	1	1
Lymphoid Hyperplasia	++								++	++	++	++
Dog Number	1,081	1,072	1,093	1,118	1,073	1,087	1,088	1,108	1,112	1,113	1,122	1,129
Dose (mg/day)	0	0	0	0	0	0	0	0	0	0	0	0

NO CHANGES

+ = Increase
1 + moderate
- = Decrease

Rating of changes
2 + marked
No entry = no visible lesion
(+) very slight
3 + severe

(+) slight
4 + very severe

I. EXECUTIVE SUMMARY

Introduction

Over the past half decade, hexachlorobenzene (HCB) along with DDT and mercury have become synonymous with environmental contamination. Important industrial and agricultural applications and a resistance to biodegradation have combined to insure a widespread pattern of distribution, including human food sources such as fish (Kaeman, *et. al.*, 1969) and domestic animals (Booth and McDowell, 1975). Field surveys of human populations (Burns and Miller, 1975) showed accumulations of HCB in fat and plasma and caused concern about potential hazardous effects.

In Turkey, HCB was inadvertently consumed by a large number of people who ate bread containing high levels of the chemical. Out of this experience came the knowledge that HCB is a potent inducer of acute hepatic porphyria in humans (Schmid, 1960), (Cam and Nigogosyan, 1963). Subsequently, a variety of other species were also susceptible to HCB porphyria including rats (Campbell, 1963), (Stonard, 1974), guinea pigs, mice (DeMatteis, *et. al.*, 1961) and quail (Vos, *et. al.*, 1971). Hepatomegaly followed exposure to toxic levels with cell swelling and focal necrosis, and, when viewed grossly or microscopically with a source of ultra-violet light (UVL), hepatocytes showed a bright red cytoplasmic fluorescence. The same response was seen in cells of embryonic hepatic tissue culture exposed to porphyrigenic agents such as griseofulvin, allylisopropylacetylcarbamide and HCB (Granick, 1965). Experimental animals and man exposed to these agents usually showed increased urinary levels of protoporphyrin, coproporphyrin and uroporphyrin. An associated condition in man, severe photosensitivity with dermal blistering and sloughing, was reproducible in rats given 0.2% HCB if bare skin exposed by plucking or shaving the overlying hair was irradiated with UVL, (Pearson and Molkinsen, 1965). This work demonstrated that HCB causes a similar porphyric response in man and the smaller laboratory animals, but information was lacking on toxicity in larger laboratory animals. Therefore, a study was undertaken in dogs administered HCB at a broad range of doses for 12 months. The results will be presented and described.

Methods

Thirty male and thirty female beagle dogs, 7-10 mo, 6.3-10.3 kg, were purchased^a free of heart worm and vaccinated against distemper, hepatitis and leptospirosis. Following acceptance, they were quarantined for 1 month and established to be in good health and free from internal and external parasites, and then divided into 5 groups of 6/sex/level and treated 7 da/wk (Table 1).

Micro-analytical grade HCB was purchased commercially^b; NMR and GLC^c indicated that the material was 99.9% pure. Microscopically, by transmitted regular and polarized light, the form was a needle shaped, rhombic crystal, showing iridescent birefringence. Bulk material was packed into hard gelatin capsules directly for administration at the highest dosage level and mixed with lactose before encapsulation for the other dose levels. Control animals were housed in a separate room and received lactose.

Body weights and temperatures were recorded weekly and, at the beginning and completion of a treatment period, each animal received a direct ophthalmoscopic examination and the oral mucous membranes and teeth were viewed by UVL.

Laboratory studies performed on all dogs twice predosing and at 4, 13, 20, 39 and 52 weeks, or whenever any animal showed a severe toxic reaction and his survival was questionable, were the following: a) hematology-Hct, Hgb, RBC, WBC, differential, platelet and reticulocyte counts and prothrombin time; b) clinical chemistry-glucose, BUN, Cl, Ca, pH, pCO₂, SGOT, SGPT, alk PO₄, serum electrophoresis, and, in the high dose animals only at wk 0, 4, 13, 20 and 39, total serum lipids, triglycerides and cholesterol; c) complete urinalysis, during treatment, included pH, SpG, glucose, protein, bilirubin, sediment exam, and ketones.

All routine clinical chemistry and hematology followed standard procedures. Total serum lipids were measured colorimetrically (Bucolo and Davie, 1973). Cholesterol by using commercial reagent kits which employ the Lieberman-Burchard reaction. Serum insulin was measured in 6 dogs by radioimmune assay utilizing I¹²⁵ competition with endogenous insulin for binding sites on latex particles coated with insulin antibody. Total protein was determined by the biuret method (Gornall, 1949).

a. Marshall Research Animals Inc, North Rose, N.Y.

b. BDH Chemicals Ltd, Poole, England.

c. Performed by Dr. J.L. Laseter, Univ. of New Orleans, La.

TABLE 1 DOSE AND NECROPSY SCHEDULE

<u>Group#</u>	<u>No. of Animals</u>		<u>Dosage Levels</u>		<u>Necropsy Schedule</u> (number/sex/level)	
	<u>male</u>	<u>female</u>	<u>ppm</u>	<u>mg/day</u>	<u>Interim</u> (5 mo.)	<u>Final</u> (12 mo.)
Control*	6	6	0	0	2	4
2	6	6	2.5	1.0	2	4
3	6	6	25.0	10.0	2	4
4	6	6	250.0	100.0	2	4
5	<u>6</u>	<u>6</u>	2500.0	1000.0	<u>2</u>	<u>4</u>
	30	30			10	20

*Lactose in gelatin capsules

Cellulose acetate electrophoresis followed the Gelman, (1968) procedure. Delta-aminolevulinic acid (ALA) levels were determined in acidified, twenty-four hour collections of urine from six dogs using commercial reagent kits^a.

All dogs were necropsied and organs examined grossly. Liver tissue was frozen, sectioned, and examined by fluorescence microscopy. Bile and perirenal adipose tissue samples were analyzed for HCB as will be described. The following tissues from all dogs were fixed in 10% neutral buffered formalin: testis, cecum, mammary gland, brain, pituitary, thoracic spinal cord, duodenum, jejunum, ileum, large intestine, urinary bladder, prostate, eye, thyroid, lung, heart, liver, gall-bladder, spleen, kidneys, adrenals, stomach, ovary, uterus, skin, bone marrow, sciatic nerve, salivary gland, mesenteric lymph node, pancreas and any unusual gross lesions. Paraffin sections of these tissues were cut at 6 μ m, stained with H&E and examined microscopically.

Rat Porphyrrogenic Bioassay

The porphyrrogenic potential of the lot of HCB under study was established in a short term feeding study in 4 male and 4 female C/D rats^b, 200-250 gms, fed 0.2% HCB. Four additional rats served as controls and consumed untreated ground feed. After 5 and 10 wks of treatment, 2/sex/level were necropsied. The following organs were examined in situ by UVL: bone and bone marrow, liver, biliary system and upper duodenum. Fresh liver impression smears and 4 μ m frozen sections were made as well as blood and bone marrow films, and examined microscopically with UVL between 320 and 450 μ m.

Hexachlorobenzene Tissue Analysis

The methods are described elsewhere (Crist, et. al., 1975). Briefly, bile and adipose tissue were first extracted in hexane and then semi-purified in Florisil[®] columns. HCB analysis was by GLC using a Varian Aerograph Model 204 with a flame ionization detector for measuring levels above 10 ppm and a Model 1400 with a tritium foil electron capture detector for levels between 10 ppm and 10 ppb.

a. Analyzed by Leary Laboratories, Boston, Mass.

b. Charles River Breeding Laboratories, North Wilmington, Mass.

Hematology and Clinical Chemistry Procedures

1. Hematologic Determinations:

Hematocrit (%)

Hemoglobin (gm %)

RBC ($10^6/\text{mm}^3$)

WBC ($10^3/\text{mm}^3$)

All these determinations were performed according to the Instruction Manuals for the Model "F" Coulter Counter; RBC/Hct Computer and Hemoglobinometer attachment which works in conjunction with the Coulter Counter. (Coulter Electronics, Inc., Hialeah, Florida).

WBC

Differential (%)

Slide fixation and staining was performed by a modification of the technique of Wright using an Ames Hema-Tek Automatic Slide Stainer. Cell counting and identification was made by light microscopy. (Wintrobe, M.M., Clin. Hematology, Lean and Febiger, Philadelphia, 4th ed., p. 406).

Reticulocytes (%RBC)

The staining method of Brecher using the new methylene blue dye was applied. Counting was by light microscopy. (Amer. J. Clin. Path. 19: 895, 1949).

Platelets ($10^3/\text{mm}^3$)

Cells were stained by a modification of the procedure of Rees-Ecker, (Tocantins, L.M., Arch. Path. 23: 850, 1937).

2. Blood Chemical Determinations:

BUN (mg %)

The reaction of urea with diacetyl monoxime in

Glucose (mg%)	Glucose 50 µl serum) Formation of a green colour complex between adohexoses and primary aromatic amine by using 6% O-toluidine in glacial acetic acid. (Ref. Dubowski, K.M., Clin. Chem. <u>8</u> : 215, 1962).
AP *	Alkaline phosphatase in King Armstrong units/ml serum according to the method of King, E.J. and Armstrong, A.R., Canad. M.A.J. <u>31</u> : 376, 1934.
SGOT ** SGPT **	200 µl serum for each test. Measured by colorimetric method according to Reitman and Frankel (Am. J. Clin. Path. <u>28</u> : 56-63, 1957). End product of the reaction is reacted with dinitrophenyl hydrazine to form hydrozone complex, which give a colour complex with an alkaline, and quantified spectrophotometrically.
Cl ⁻	Chloride in serum (20 µl) Radiometric method according to Instruction Manual for CMTIO chloride Titrator by Radiometer AIS. Copenhagen, Denmark.
Insulin	Serum insulin is measured as it competes with I ¹²⁵ insulin for binding sites on antibody coated latex particles. Results are measured as µU/ml.

* Multiply by 3.53 to obtain International units

** Multiply by 0.482 to obtain International units

Protime	Prothrombin time (seconds), determined according to the procedure of Quick, A.J., Amer. J. Clin. Path. <u>10</u> : 222, 1940.
Bilirubin (Total and Direct)	(mg%, 200 μ l serum), Reaction of free and conjugated bilirubin with Diazo Reagent in alkaline and acid mediums. (Jendrassik, L., and Grof, P., Biochem. <u>2</u> : 797: 81-89, 1938).
Ca ⁺⁺ *	Calcium (mg%, serum), complex formation with calcein and fluorometric determination. (Bett, I.M. and Fraser, G.P., Clin. Chem. Acta. <u>4</u> : 346-356, 1956).
pCO ₂ , pH	Measured in whole blood by a IL 313 Blood Gas Analyzer. Results are expressed in pH units, and, for pCO ₂ , meq/l and mm Hg.
Total Lipids	Colorimetric method based on the sulfo-phospho-vanillic reaction (Am. J. Clin. Path. <u>5</u> : 89-91, 1970). Results are in mg%.
Triglycerides	Enzymatic method of Bucolo and David (Clin. Chem. <u>19</u> : 476, 1973). Results are in mg%.
Cholesterol	Commercially prepared kits which are based on the Lieberman-Burchard reaction; results are in mg%.

* Divide by 1.2 to obtain MEQ/L.

Results

Rat Porphyrogenic Bioassay

After 5 weeks of consuming 0.2% HCB female rats showed no gross organ fluorescence under incident UVL. Microscopically, frozen liver or liver imprints emitted a bright red fluorescence with transmitted UV light. After 10 weeks, fluorescence was grossly visible in the liver, cortical bone and the lumen of the upper duodenum. Microscopically, liver fluoresced; however, bone marrow did not. The treated male rats showed none of these signs. Since this reaction is specific for porphyrins (Pathak and Burnett, 1964), the material was confirmed to be porphyrogenic.

Bile and Adipose Tissue Levels of HCB

Fat and bile samples were analyzed for HCB as a measure of absorption and accumulation. A time and dose-related increase established that gastrointestinal absorption and storage occurred at all levels including the lowest (Table 2).

Canine Toxicology

1. Mortality and Body Weight

The chronic administration of HCB 1000 mg/da, caused intermittent diarrhea, anorexia (Table 3) and a progressive overall weight loss of 23%. Six dogs died or became moribund after 43, 79, 79, 88, 227 and 299 days. The surviving dogs body weight stabilized after approximately 15 weeks and either remained constant or was recovered during the ensuing weeks of continued administration. Two female dogs receiving 100 mg/day had reduced food consumption and weight loss. One died on the 52nd day after losing 2.5 kg; the second died on day 298 following a 2.1 kg weight loss. Other weight changes in the dogs which survived the 2 highest doses for the complete study, ranged from losses of 1-4 kg, to gains of 1-2 kg. The gains in body weight for dogs receiving 10, 1 or 0 mg/dog/day were similar (Table 4).

TABLE 2 HCB IN TISSUES OF TREATED DOGS

Daily Dose (mg)	Weeks On Test	Average Per Group			
		Cumulative Dose (gm)	Bile (ppm)	Adipose Tissue	
				Total (ppm)	Lipid Extracted (ppm)
1,000	4-20	85.80	72	958	2,363
1,000	20-50	387.20	50	1,216	1,736
100	4-20	12.02	60	163	433
100	20-50	38.00	87	714	2,309
10	4-20	1.46	3	69	105
10	20-50	3.73	4	67	84
1	4-20	.15	0.19	7	12
1	20-50	.37	0.52	11	18
0	4-20	.00	0.00	.10	.15
0	20-50	.00	0.06	1.05	1.43

TABLE 3: ADVERSE CLINICAL SIGNS IN BEAGLE DOGS TREATED WITH HEXACHLOROBENZENE (HCB)
NUMBER OF OBSERVATIONS PER SEVEN DAY WEEK

Week No.	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	
Dog No.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.	Anorex.	Diarh.
1,000 mg/Da																												
1070																												
1075	1	2		3	1	4	3	1	3	1	2	2	1	4	1	3	2	1		1		1	3	2	1	1	1	
1075	4	3		3	5	6	7	7	7	7	7	2	4	7	5	2	3	5	2	1	3	1	7	2	7	4	6	
1077	2	1		1	1	2	1	3	3	2	3	2	1	Died	3	2											3	
1089																												
1089	5	4	1	7	1	5	Died	3	1	2	3	1	2	3	2	1		2	2	3	2	3	2	4	3	3	2	
1096																											1	
1098	2	1		1	1	2	4	3	1	3	2	1	4	1	7	3	2										1	
1100	5	1	6	2	1	5	6	7	4	7	7	6	5	6	5	2	3	1	1	1	3	2	3	2	1	1	1	
1104	2	1	2	1	3	2	4	4	4	3	3	1	5	3	5	4										6	1	
1107																		1	2	1	4	2	4	1	6	3	2	
1109																											1	
1115																											1	
1128	5	3	3	5	2	2	1	5	5	7	3	3	2	5	5	2	1	5	1	2	4	5	2	1	Sacrificed			
100 mg/Da																												
1076	3	6	3	6	1	3	5	5	1	5	6	3		4	3	2	1	3	1	1	1	2	2	Sacrificed				
1079																												
1082																												
1083	1																											
1085																												
1091																												
1102	3	2																										
1110																												
1114	4	5	6	7	2	4	2	6	1	2																		
1121																												
1123																												
1127																												

10 mg/Da No Adverse Signs
1 mg/Da No Adverse Signs
Control No Adverse Signs

TABLE 3:(CONT.) ADVERSE CLINICAL SIGNS IN BEAGLE DOGS TREATED WITH HEXACHLOROBENZENE (HC8)
NUMBER OF OBSERVATIONS PER SEVEN DAY WEEK

Week No.	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	43	44	45	46	47	48	49	50	51	52	53	54
Dog No.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.	Diarrh.	Anorex.
1,000 mg/Da																											
1070	3						1	1	1	1	1	2		1		1		3	3			1					3
1075	4	6	7	5	5																						
1077																											
1089	1	1	1	1			3	1	2	1	3	5	1	2	2			2	1		1						3
1096																											
1098	2																										
1100	2	1	3	1	1		1	3	1	6	2	1	5	1	4	1		1	1	4							3
1104																											
1107																											
1109	1																										1
1115																											1
1128																											1
100 mg/Da																											
1076																											
1079																											
1082																											
1083																											
1086																											
1091	1																										3
1102	2	2	3	3	1		1	3	3	2	2	2	3	1	5	3	7	2	6	1							2
1110																											
1114																											
1121																											
1123																											
1127																											

10 mg/Da No Adverse Signs
1 mg/Da No Adverse Signs
Control No Adverse Signs

TABLE 4: AVERAGE WEEKLY BODY WEIGHTS (kg) OF DOGS CONSUMING HEXACHLOROBENZENE (HCB)
HCB CONSUMPTION (mg/Dog/Day)

Study Week	Control		1		10		100		1000	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
0	10.2	7.7	9.7	8.0	9.9	7.7	9.5	7.6	9.2	7.9
1	10.2	8.0	9.9	8.0	9.8	7.6	9.7	7.8	9.7	7.4
2	10.4	8.0	9.9	8.1	9.8	7.6	9.7	7.8	9.5	6.9
3	10.7	8.4	10.2	8.5	9.7	7.6	9.7	7.5	9.6	6.7
4	10.2	8.3	10.1	8.4	9.8	7.8	9.7	7.8	8.9	6.4
5	10.3	7.9	10.1	8.1	9.8	7.9	9.9	7.7	9.5	6.5
6	10.4	8.1	10.4	8.5	10.2	7.9	10.0	7.7	9.3	6.7
7	10.6	8.5	10.5	8.6	10.1	7.6	9.5	7.4	9.2	6.5
8	10.7	8.7	10.4	8.5	10.3	8.1	10.2	9.0 *	8.9	6.4
9	10.6	8.2	10.5	8.4	10.6	8.1	10.4	8.6	8.6	6.3
10	10.2	8.4	10.5	8.8	10.6	7.9	10.5	8.7	8.0	6.2
11	10.7	8.7	10.8	8.8	10.7	8.1	10.2	8.6	7.3	6.0
12	10.6	8.5	10.5	8.7	10.7	8.1	10.4	8.8	8.1 **	6.1
13	10.1	8.5	10.3	8.4	10.7	8.1	10.6	8.8	9.0 *	6.1
14	10.1	8.5	10.8	8.8	10.4	7.9	10.7	8.8	8.3	5.7
15	10.1	8.5	10.8	8.8	10.9	7.9	10.5	8.7	8.1	5.8
16	10.5	8.8	10.8	8.8	11.0	8.1	10.0	8.5	8.4	6.1
17	10.6	8.9	10.7	8.9	10.8	8.1	9.8	8.4	8.4	6.3
18	10.4	9.0	10.6	8.9	10.7	8.2	10.2	8.8	8.3	6.1
19	10.6	9.2	10.6	8.8	10.8	8.3	10.3	8.7	8.5	6.4
20	10.7	9.3	10.4	8.9	11.0	8.2	10.6	8.9	8.6	6.4

* Smallest animal died, increase in average weight reflected by this loss.

** Two smaller animals died, increase in average weight reflected by this loss.

TABLE 4: AVERAGE WEEKLY BODY WEIGHTS (KG) OF DOGS CONSUMING HEXACHLOROBENZENE (HCB)
HCB CONSUMPTION (mg/Dag/Day)

Study Week	Control		1		10		100		1000	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
21	10.8	9.5	10.4	9.0	11.7	8.2	11.1	9.2	8.6	6.7
22	10.3	9.9	10.7	9.2	11.6	8.1	10.9	9.1	8.3	6.6
23	10.6	9.9	11.2	9.3	11.5	8.2	10.9	9.2	8.6	6.2
24	10.5	9.6	10.5	9.1	11.3	7.7	11.0	9.3	8.3	6.0
25	10.4	9.7	10.6	9.2	11.5	8.1	10.8	9.1	8.1	5.7
26	10.2	9.6	10.6	9.3	11.6	8.0	10.8	9.1	8.2	5.9
27	10.1	9.5	10.4	9.1	11.4	7.9	10.5	8.8	8.0	5.9
28	10.2	9.7	10.5	9.3	11.5	8.1	10.7	9.0	8.1	5.9
29	10.2	9.7	10.5	9.4	11.6	8.2	10.7	9.1	7.7	6.3
30	9.9	9.7	10.4	9.4	11.4	8.1	10.6	9.2	7.5	7.4
31	9.9	9.7	10.2	9.6	11.3	8.2	10.2	9.0	7.5	6.5
32	9.9	9.6	10.4	9.4	11.4	8.3	10.5	9.1	7.3	6.4
33	10.0	9.8	10.5	9.5	11.2	8.0	10.6	9.1	8.4	6.4
34	10.0	9.8	10.5	9.5	11.4	8.7	10.7	8.9	8.3	6.3
35	10.0	9.8	10.5	9.5	11.4	8.6	10.8	9.0	8.2	6.2
36	9.9	9.7	10.5	9.5	10.6	8.4	10.5	8.9	7.9	5.8
37	9.5	10.5	10.5	9.5	11.2	8.3	10.6	8.8	8.2	6.1
38	9.9	10.0	10.3	9.5	11.3	7.8	10.7	8.7	8.2	6.0
39	10.0	10.0	10.4	9.5	10.1	8.3	10.8	8.8	8.4	6.0
40	9.9	10.0	10.5	9.5	11.3	8.5	10.8	8.7	8.3	6.0
41	9.9	10.0	10.5	9.7	11.3	8.6	10.8	8.8	8.5	6.3
42	9.9	10.0	10.4	9.4	11.2	8.3	10.8	8.5	8.4	6.2
43	9.8	9.9	10.6	9.7	11.2	8.4	10.7	10.0	8.2	6.5
44	9.8	10.0	10.4	9.6	11.3	8.7	11.0	9.9	8.3	6.5
45	9.5	9.8	10.3	9.5	11.3	8.5	10.7	9.6	8.2	6.4
46	9.6	9.9	10.4	9.5	11.1	8.6	10.6	9.6	8.2	6.5
47	9.9	9.9	10.2	0.5	11.1	8.4	10.6	9.5	8.2	6.6
48	9.5	10.0	10.3	9.7	11.1	8.5	10.5	9.3	8.1	6.5
49	9.6	10.1	10.2	9.6	11.2	8.7	10.6	9.3	8.2	6.9
50	9.7	10.0	10.3	9.5	11.0	8.6	10.4	9.2	8.2	6.8

2. Clinical Observations

The most apparent dose and time related adverse response detected by blood analyses was an absolute granulocytosis with a stable level of lymphocytes in animals at the 2 highest dose levels. Out of 12 dogs at each dose level, 9 receiving 1000 mg/da and 7 receiving 100 mg/da had at least 1 episode of a significant neutrophilia. The highest dose group was above normal ($p < .05$) after 4 wks and remained elevated throughout the study (Figure 1). Neutrophil counts in the group receiving 100 mg/da were normal for the first 4 wks, then rose slightly above the upper limits during the ensuing 16 wks and, finally, reached a point at 50 wks almost twice the maximum range of normal (Figure 1). This was largely an afebrile response. In a total of 29 separate observations in 16 dogs, significant neutrophilia and a body temperatures greater than 102°F were observed together only twice. The neutrophil levels for the remaining dogs were unchanged.

A hepatotoxic effect was suggested by alkaline phosphatase elevations which occurred in 5 dogs receiving 1000 mg/da and 2 at 100 mg/da. This was sustained in D1100F at 100 mg/da from day 79 through necropsy on day 298. The remaining 4 dogs showed terminal elevations. Further hepatic effects were isolated SGOT elevations in 4 dogs, 2 from each dosage group, terminally in 2 dogs and self-correcting in 2.

The remaining abnormal laboratory findings were confined to the highest dose level and 2 dogs which died after receiving 100 mg/da for 8 and 42 weeks. This group of animals also had anorexia and severe body weight loss. Therefore, the abnormal findings (incidence in parenthesis) hypoglycemia (5), hypocalcemia (4), and anemia (2) may have been secondary to malnutrition and inanition. Serum triglycerides (Table 5), measured in the highest dose level group only, responded in a time related manner early in the study with an increase over baseline values, but returned to normal with continued treatment. Serum insulin levels were assayed in 4 dogs to determine if hyperinsulinism might be causing hypoglycemia. An inverse relationship between insulin and blood glucose suggested that altered pancreatic function and the hypoglycemia were unrelated (Table 6). Urine ALA was similar in 3 control females and 3 females treated with 1000 mg/da for 5 months (Table 7).

Fig. 1: CHANGES IN THE BLOOD NEUTROPHILS OF DOGS RECEIVING HCB

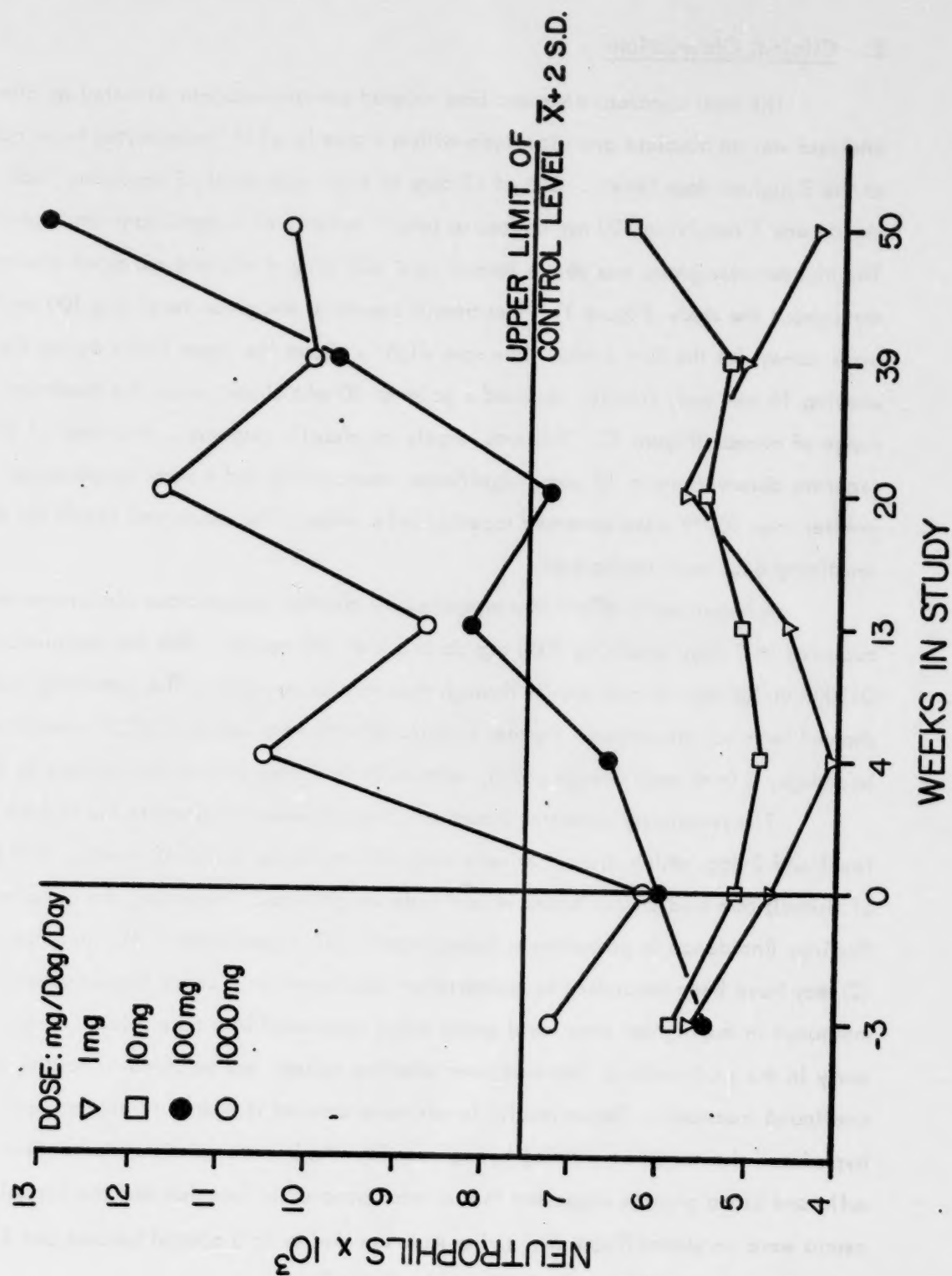


TABLE 5
SERUM LIPID PROFILE: DOGS RECEIVING 1,000 MG/DOG/DAY HCS

Dog #	0 Week			4 Weeks			13 Weeks			20 Weeks			39 Weeks		
	Total Lipids mg/100 ml	Triglycer. mg/100 ml	Cholest. mg/100 ml	Total Lipids mg/100 ml	Triglycer. mg/100 ml	Cholest. mg/100 ml	Total Lipids mg/100 ml	Triglycer. mg/100 ml	Cholest. mg/100 ml	Total Lipids mg/100 ml	Triglycer. mg/100 ml	Cholest. mg/100 ml	Total Lipids mg/100 ml	Triglycer. mg/100 ml	Cholest. mg/100 ml
1070	540	33	182	600	34	220	682	83	175	658	50	231	530	22	183
1075	490	18	190	600	41	260	704	64	223	552	51	258	645	36	256
1089	596	25	219	525	30	230	954	53	280	300	52	300	700	79	272
1128	555	38	193	850	67	270	784	79	265	626	38	313	-	-	-
1098	470	40	164	625	44	230	647	137	163	627	43	287	710	29	278
1100	505	43	163	350	35	110	647	64	150	532	68	273	480	56	145
1104	482	62	184	825	94	250	920	78	295	606	41	265	520	53	188
1109	552	20	185	525	25	280	511	68	150	405	49	178	470	20	178
1107	533	16	206	700	15	230	341	95	77	-	-	-	-	-	-
1077	485	45	228	625	50	270	665	197	169	-	-	-	-	-	-
1115	495	14	146	575	11	210	-	-	-	-	-	-	-	-	-
1096	512	35	228.	600	36	240	-	-	-	-	-	-	-	-	-
X =	518	32	191	616	40	223	693	92	195	584	49	263	579	42	215

TABLE 6 INSULIN LEVELS IN DOGS *

Dog Number	Treatment	Insulin Concentration ** (μ U/ml)
1114	HCB 100 mgs/day	5
1096	HCB 1000 mgs/day	4.5
1100	HCB 1000 mgs/day	12
1077	HCB 1000 mgs/day	12
1113	Lactose	20
1072	Lactose	14

* All determinations were made on fasting blood samples.

** Results represent the average of 2 determinations per sample as measured by radioimmunoassay.

TABLE 7 URINARY DELTA-AMINOLEVULINIC ACID LEVELS
IN FEMALE DOGS TREATED WITH HCB FOR FIVE MONTHS

Dog Number	Dose Level (mg/Day)	Aminolevulinic Acid Levels In Urine (mg/24 hr)
1104	1,000	.149
1098	1,000	.180
1100	1,000	.130
		$\bar{X} = .153$
1122	0	.144
1088	0	.132
1108	0	.153
		$\bar{X} = .143$

3. Gross and Microscopic Examination of Tissues

1000 mg/day: At the 1 year interval in this experiment, among the 12 dogs treated with HCB at 1000 mg/da, 2 died on days 79 and 277 respectively (1077M and 1075M); 3 were sacrificed in moribund condition on days 43, 79 and 88 respectively (1096F, 1077M and 1107M); 3 were sacrificed in poor condition on days 143, 299 and 387 respectively (1128F, 1100F and 1104F); 3 were sacrificed in fair condition between days 385 and 389 (1070F, 1098F); and 1 was sacrificed in good condition on day 387 (1109M). Important HCB related lesions were observed in a variety of tissues including omentum, serosal surfaces of the abdomen, stomach and vascular system. Specific lesions included focal omental necrosis, fibrosis and subacute serositis-steatitis; fibrous intestinal adhesions and proliferative abdominal serositis; focal lymphoid hyperplasia in the mucosa of the pyloric antrum and fundus of the stomach; and a disseminated segmental necrotizing arteritis periarteritis resembling periarteritis nodosa. Additional lesions included generalized muscular atrophy of all axial and appendicular muscle groups, amyloidosis affecting the spleen and mesenteric lymph nodes, focal bronchopneumonia, fatty change in the liver, lymphoid atrophy, focal testicular degeneration, ascites and hemothorax. Specific details on these animals are given in the appendix under Necropsy and Pathology Reports.

Dog 1096F was sacrificed on day 40 in moribund condition. At necropsy, the dog was extremely thin, moderately dehydrated with a dry scurfy hair coat, a fecal soiled perineum and generalized atrophy of all axial and appendicular muscle groups. Additional lesions included the following: In the coronary grooves on the posterior and lateral sides of the heart several focal, firm, slightly raised 0.5 x 1.0 x 0.8 mm dark red areas were observed. Numerous focal petechial hemorrhages were present in the mucosa of the urinary bladder. The mucosa of the stomach showed multiple focal 0.5 mm erosions with tags of dark red-brown blood attached. The mucosa of the small intestine had focal reddish areas covered with a bile stained heavy mucus pellicle. Present on the mucosa throughout the entire small intestine were shiny yellow HCB-like crystals approximately a hair's width in diameter and 5 mm long. No formed

feces were in the colon and that which was present was pasty, mucoid and green-brown. Subdural hemorrhage was noted along the spinal cord between cervical vertebrae 4 and 7. The vertebral column and intervertebral discs in the area appeared to be normal. The most remarkable microscopic finding was a severe, disseminated, segmental subacute necrotizing vasculitis-perivasculitis which affected arteries and arterioles in virtually all organs of the body. Specifically focal blood vessels in the following organs were affected: heart, mediastinum, esophagus, stomach, small and large intestine, thyroids, adrenals, mammary gland, lymph nodes, urinary bladder, spinal cord, meninges, brain, bones and eyes. Inflammatory cells observed in the walls and periadventitial tissues of affected vessels included polymorphonuclear leukocytes, macrophages, lymphocytes and plasma cells. In focal segments of arterioles, the walls of vessels appeared as a homogeneous eosinophilic coagulum resembling fibrinoid necrosis. The intima of many vessels showed a proliferative endarteritis. In the heart and liver, portions of the parenchyma adjacent to affected blood vessels showed subacute inflammation. In addition, focal areas of the ventricular myocardium showed pronounced interstitial fibrosis. An organized recanalized thrombus was observed in a large mediastinal artery. Amyloidosis affected the lymphoid nodules in the mesenteric lymph node and spleen. The pink homogeneous material present was slightly positive with congo red stain and showed slight green birefringence with polarized light which are positive features of amyloid. Myeloid hyperplasia was characterized by marked hypercellularity of the bone marrow.

Dog 1115M was sacrificed on day 79 in moribund condition. At necropsy, the dog was extremely thin, with a dry scruffy hair coat, a face soiled by ocular discharge, a fecal soiled perineum and marked alopecia along the eyelid margins. Significant gross and microscopic lesions in this animal included, bilateral hemothorax (100 cc), severe focal acute bronchopneumonia, slight diffuse fatty change in the liver, accumulations of green pigment in Kupffer cells in the liver and marked lymphoid atrophy affecting pancreatic, mesenteric and colonic lymph nodes, Peyer's patches and the spleen.

Dog 1077M was sacrificed in moribund condition on day 79. At necropsy, the dog was moderately dehydrated, emaciated with generalized atrophy of all muscle groups and showed epiphora with soiling of the face near the medial canthus of each eye. Drug-related lesions included marked to severe focal omental necrosis, fibrosis and subacute serositis-steatitis; marked lymphoid atrophy affecting the tracheal lymph node, thymus, spleen and Peyer's patches; marked centrilobular fatty change; slight focal epithelial erosion of the esophagus and subacute vasculitis-perivasculitis affecting the liver and tracheal lymph node. Grossly, the falciform ligament still contained fat, although there was essentially no subcutaneous fat. The omentum, instead of being a free skein, was condensed and drawn together and there were old fibrous adhesions in the serosa of the colon. Microscopically, much of the omental fat was normal in appearance, however a sizable portion had a bubbly mucinous-like appearance and was criss-crossed by fibrous bands composed of rapidly replicating fibroblasts and new collagen. A subacute perivasculitis affected small blood vessels within the fat which were surrounded by mononuclear inflammatory cells primarily lymphocytes and plasma cells. On the serosal surfaces of the fat there was focal serosal hyperplasia and focal areas of necrosis characterized by marked eosinophilia and the exudation of many polymorphonuclear leukocytes and mononuclear cells.

In the gross dissection, the splenic capsule was wrinkled, the edges were sharp and on section lymphoid nodules could not be seen. Microscopically, lymphoid nodules in the spleen and other lymphoid tissues were smaller and less cellular than normal.

In the gross dissection, an erosion of the esophageal mucosa occurred in the distal esophagus near the cardia and was 3.8 x 1.6 x 0.05 cm. The crater of the erosion was gray. Microscopically, no inflammation was observed in the area; however, there was desquamation of the covering epithelium.

Microscopically, the liver demonstrated a marked centrilobular fatty change which was oil red O positive and appeared as variable sized multivacuolation of hepatocytes around central veins. Also noted in the liver was a focal, segmental, subacute vasculitis-perivasculitis affecting scattered blood vessels. The inflammatory cells

involved consisted primarily of lymphocytes and occasional polymorphonuclear leukocytes and plasma cells which were both within the walls of vessels and in the adventitia around them. A similar focal segmental subacute vasculitis-perivasculitis with fibrinoid necrosis was noted in the tracheo-bronchial lymph node.

Dog 1107M was sacrificed on day 88 in moribund condition. At necropsy, the dog was emaciated and showed generalized atrophy of all axial and appendicular muscle groups. Significant drug-related lesions in this dog included severe focal acute bronchopneumonia, marked centrilobular fatty change, moderate focal subacute perivasculitis within the omental fat, moderate focal proliferative serositis and serosal fibrosis affecting bowel segments and the urinary bladder, moderate lymphoid atrophy and focal testicular degeneration. It is not clear whether the latter lesion is drug-related.

Gross lesions were pulmonary edema and consolidation, fibrous adhesions between bowel loops and the mesentery and condensation and folding of the omentum upon itself. Microscopic features of the above lesions were similar to those previously described with the addition of proliferative serositis, serosal fibrosis, hemorrhage and neocapillary formation affecting the duodenum, jejunum, ileum, cecum and urinary bladder.

Dog 1128F was sacrificed in poor condition on day 143. The dog was very thin, had a dry scurfy hair coat and generalized atrophy of all muscle groups. Focal alopecia was noted at the medial canthi of the eyes, along the margins of the eyelids and around the tubercles. The face near the medial canthus of each eye was covered with scabs and exudate. Drug-related lesions included: ascites (35 cc); proliferative, serositis and fibrosis affecting the visceral peritoneum of all portions of the bowel, urinary bladder and pancreas; and focal omental fibrosis and subacute steatitis.

At necropsy all portions of the bowel were tightly adherent to each other by firm fibrous adhesions which resulted in a consolidated mass at the base of the mesentery. The omental fat was consolidated into a small firm mass approximately 6 x 5 x 2 cm attached to the lesser curvature of the stomach. Microscopic features of the above

lesions were similar but more severe than those previously described.

Dog 1075M died on day 227 in a very poor emaciated condition. The hair coat was dry and scurfy and there was a slimy discharge adherent to the medial canthi of the eyes. A 2 cm² decubital sore was present on the lateral surface of the right hock. The abdomen contained approximately 10 cc of pale straw colored fluid. The omentum was fibrosed, condensed in size, and contained a very small quantity of fat. Focal fibrous adhesions were noted between the bowel and mesentery. Important microscopic lesions included a periarteritis nodosa-like arteritis with fibrinoid necrosis and subacute perivasculitis affecting arterioles in the esophagus, trachea and omentum; focal omental fibrosis and granulomatous inflammation; focal colonic chronic serositis; and lymphoid atrophy affecting the thymus, mesenteric lymph nodes and Peyer's patches. Additional lesions included severe periesophageal granulomatous inflammation and peritracheal abscess formation which may be related to the vascular lesions observed in these organs. Slight testicular degeneration and focal subchronic meningitis affecting the brain were also observed.

Dog 1100F was sacrificed in emaciated poor condition on day 299. Grossly the omentum was condensed and tightly adherent to the descending colon. The liver was large, had a nutmeg appearance and was extremely friable. Important drug-related lesions in this dog included: a periarteritis nodosa-like arteritis with hyalinization and perivasculitis affecting arterioles and arteries in the mediastinal lymph nodes, urinary bladder, ovarian bursa, omentum and peritracheal tissues; omental fibrosis, necrosis, and fat atrophy; and subacute hepatitis with bile duct hyperplasia and chronic pericholangitis.

The remaining dogs (1070F, 1104F, 1109M, 1098F and 1089M) were sacrificed in poor to good condition between days 385 and 389. HCB related lesions in these dogs were limited to varying degrees of fibrous adhesions between the omentum and visceral peritoneum covering the stomach, mesentery, small and large intestines and liver; and lymphoid hyperplasia affecting the pyloric antrum and fundic mucosa of the stomach. Each dog showed some evidence of epiphora with varying degrees of gray-brown or clear secretion matted in the hair near the medial canthus of the eyes.

Incidental pathological changes observed in the above dogs in various combination included the following: hematocyst on the septal cusp of the right AV valve, focal pulmonary granulomas, focal subacute proliferative pleuritis and pleural fibrosis (probably related to pulmonary nematodes), focal granulomatous lymphadenitis in the mesenteric lymph nodes, focal subacute pericholangitis, interstitial pancreatitis and interstitial prostatitis, focal arteriosclerosis in the coronary arteries, focal mineralized casts in collecting tubules; focal cysts in the thyroid, pituitary and parathyroid; and focal acinar atrophy in the periurethral prostate.

100 mg/day: At the 1 year interval in this experiment, among the 12 dogs treated with HCB at 100 mg/day, 1 died on day 298 (1102F); 2 were sacrificed in poor condition on days 52 and 381 respectively (1114F and 1082F); 1 was sacrificed in fair condition on day 380 (1083M); 5 were sacrificed in good condition on days 377 and 381 (1123M, 1083M, 1086F, 1091M, 1110F and 1079M); and 3 were sacrificed in excellent condition on day 144 (1076F, 1121M, 1127M). HCB related lesions observed in these dogs included: focal acute hemorrhagic bronchopneumonia; generalized lymphoid atrophy; marked to severe hyperplasia of gastric lymphoid tissue particularly affecting the pyloric antrum but also extending along the lesser curvature into the body, or in some cases affecting the pyloric canal, fundus or cardia; inflammatory lesions in the abdomen including atrophy of omental fat and omental subacute steatitis, fibrosis, or fibrous adhesions and hepatic involvement in one dog (1102F) with bile duct hyperplasia, chronic pericholangitis and slight fatty change. Specific details on these animals are given in the appendix under Necropsy and Pathology Reports.

Dog 1114F was sacrificed in poor condition on day 52. At necropsy the dog was emaciated with pale mucous membranes, a dry coat and fecal soiling of the hind-legs. Significant HCB related lesions included severe focal acute hemorrhagic bronchopneumonia, moderate to severe lymphoid atrophy affecting the thymus, tracheal, bronchial, mesenteric, mediastinal and parotid lymph nodes, and Peyer's patches.

Dogs 1127M, 1121M and 1076F were all sacrificed in excellent condition on day 143. HCB related lesions in these dogs were limited to pronounced lymphoid

hyperplasia in the pyloric antrum and fundic regions of the stomach. Dog 1076F also demonstrated slight hyperplasia of lymphoid tissue in the esophagus and dog 1127M had some large lymphoid nodules in the submucosa of the ileum. The stomach of each dog in the fundic and pyloric antrum areas was covered with many 2-4 mm slightly raised and coalescent nodules. In general, the body of the stomach was fairly free of these nodules, although occasionally a few could be seen in the esophageal mucosa. Microscopically, the lymphoid nodules in the fundus and pyloric antrum were large and well developed. Lymphoid nodules in the body of the stomach were fewer, smaller and much less prominent.

Dog 1102F died in emaciated condition on day 298. Drug-related lesions in this dog included: omental fibrosis, subacute steatitis and fat atrophy; subacute hepatitis, bile duct hyperplasia, chronic pericholangitis, and fatty change; severe serosal fibrosis of the rectum; generalized lymphoid atrophy and focal bronchopneumonia.

Dog 1082F was sacrificed in poor condition on day 381. HCB related lesions in this dog were limited to evidence of chronic inflammation in the abdomen with marked omental fibrosis and severe fibrous adhesions between the omentum, mesentery, and visceral peritoneum covering the gastrointestinal tract, liver, spleen and pancreas. In addition marked hyperplasia of lymphoid tissue was noted in the mucosa of the fundus and pyloric antrum of the stomach.

Important lesions in the remaining dogs (1123M, 1083M, 1086F, 1091M, 1110F, 1079M) sacrificed in fair to good condition between days 377 and 381 included lymphoid hyperplasia in the fundic and pyloric antrum areas of the stomach. Dog 1091M also showed a minor fibrous adhesion between the omentum and serosa of the ceacum. Severe prostatic atrophy and testicular fibrosis and degeneration was observed in 1079M. The relationship of the later lesions to HCB treatment is not entirely clear.

Incidental pathological changes observed in the above dogs in various combinations were similar to those seen in the dogs given 1000 mg/da of HCB with the following additions: focal granulomatous pneumonia; cross sections of nematodes in the lungs presumably Filaroides hirthi, focal subacute peribronchiolitis, thymic cysts, focal granulomas in the liver, siderofibrosis in the spleen and focal cortical hyperplasia in the

adrenals.

10 mg/day: At the 1 year interval in this experiment among the 12 dogs treated with HCB at 10 mg/da, 1 was sacrificed in fair condition on day 143 (1094F); 9 were sacrificed in good condition, 1125M on day 147, and the remaining 8 between days 371 and 374 (1103M, 1074F, 1078F, 1084F, 1120F, 1071M, 1085 and 1097M); and 2 were sacrificed in excellent condition on days 143 and 148 respectively (1117M and 1080F). HCB related lesions in these dogs were limited to lymphoid hyperplasia affecting primarily the pyloric antrum but sometimes the pyloric canal, lesser curvature of the body, cardia and fundus of the stomach. The gross and histologic features of the lesions were similar to those described in the 100 mg/da dogs. Specific details on these animals are given in the appendix under Necropsy and Pathology Reports.

Incidental pathological changes observed in the above dogs in various combinations were similar to those seen in the dogs given 1000 mg/da and 100 mg/da with the following additions: focal subacute interstitial nephritis, subacute hemorrhagic cystitis and cystic calculi.

1 mg/day: At the 1 year interval in this experiment among the 12 dogs treated with HCB at 1 mg/da, 2 were sacrificed in good condition on day 368 (1092F and 1106F) and the remaining 10 were sacrificed in excellent condition between days 148 and 364 (1105M, 1124F, 1119M, 1126F, 1095M, 1099M, 1101M, 1111M, 1116F and 1090F). Drug-related lesions were limited to moderate to marked lymphoid hyperplasia in 10/12 dogs particularly in the area of the pyloric antrum but occasionally extending along the lesser curvature of the stomach or into the cardia and pyloric canal. The gross and histologic features of these lesions were similar to those observed in the 100 mg/da dogs. Specific details on these animals are given in the appendix under Necropsy and Pathology Reports.

Incidental pathological changes seen in the above dogs were similar to those seen in the dogs given 1000, 100 and 10 mg/da of HCB with the following additions: focal subacute meningitis, focal ulceration of the soft palate, focal serosal granuloma in the colon and focal chronic hemorrhagic mediastinitis.

0 mg/day: At the 1 year interval in this experiment, among the 12 control dogs, all were sacrificed between days 146 and 350 in excellent condition. Specific details on these animals are given in the appendix under Necropsy and Pathology Reports.

Incidental pathological changes seen in the above dogs were similar to those seen in the dogs given HCB with the following additions: focal subacute epicarditis, focal cortical hyperplasia of the adrenals and a hematocyst on the septal cusp of the right AV valve.

Discussion

The severe widely disseminated arteritis affecting small arteries and arterioles was limited to 4/12 dogs at the 1000 mg/da dosage level (Table 8,9). This arteriopathy had many features suggestive of polyarteritis, hyperergic vasculitis or hypersensitivity angitis (Lehr, 1972), however, an immune reaction was not indicated by the electrophoresis results (Table 10). Similar lesions, with widely disseminated fibrinoid degeneration of small arteries and severe perivascular inflammation, have been produced clinically by a number of drugs including sulfonamides, diphenylhydantoin, iodides and thiouracil. A similar type of vasculitis has also been reported to occur in HCB treated rats (Campbell, 1963).

Bile duct hyperplasia, pericholangiolar fibrosis and inflammation, and slight fatty change in hepatocytes were found in our studies. The HCB in the bile at dose related concentrations, suggested that the ductal response may have been an irritation or direct toxic effect. In HCB induced porphyric rats, hepatomegaly, and necrosis with sparing of the biliary system was reported (Medline, et. al., 1973).

A HCB associated change was hyperplasia of gastric lymphoid nodules at all doses including 1 mg/day, one-fifth the action level guidelines. In controls 3 to 12 lymphoid nodules were grossly observed in 5/12 control beagles and microscopic evidence was present in 11. In treated groups, hyperplasia of the gastric lymphoid tissue occurred in a variable pattern to a degree of severity which always exceeded controls. The change was most prominent in the pyloric antrum but also occurred in the cardia, along the lesser curvature of the fundus and in the pyloric canal. In the most prominent cases, the gastric mucosa had a rough granular appearance and up to 400 slightly raised nodules (2 x 4 mm) were present. This probably represents a hyperplastic reaction of gastric lymphoid tissue to HCB which might reverse if the stimulus were removed. No pathophysiologic effects could be associated with this change.

Most remarkable was the lack of evidence for porphyria suggesting that the dog, unlike the rat, is insensitive to this well-known toxic effect of HCB. Several possible explanations for this species specific effect can be considered, relating to

TABLE 8: SUMMARY OF HCB RELATED RESPONSES

	Dose (Mg/Dog/Day)							
	1,000		100		10		1	
<u>General</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>	<u>No.</u>	<u>%</u>
Mortality/Morbidity	6	50	2	17	0	-	0	-
Loss of Body Weight	10	83	4	33	0	-	0	-
Anemia	2	17	0	-	0	-	0	-
Hypoglycemia	3	25	2	17	0	-	0	-
Hypocalcemia	3	25	1	8	0	-	0	-
Decreased Blood CO ₂	3	25	1	8	0	-	0	-
Lymphoid Atrophy	4	33	2	17	0	-	0	-
Neutrophilia	8	67	6	50	0	-	0	-
Polyarteritis	3	25	0	-	0	-	0	-
<u>Gastrointestinal</u>								
Anorexia, a) Dogs Showing	12	100	12	100	0	-	0	-
b) Days Shown ¹	-	32	-	19	0	-	0	-
Diarrhea, a) Dogs Showing	12	100	9	75	0	-	0	-
b) Days Shown ¹	-	8	-	3	0	-	0	-
Ascites	4	33	0	-	0	-	0	-
Serositis	4	33	0	-	0	-	0	-
Omental Adhesions	5	42	2	17	0	-	0	-
Omental Necrosis/Fibrosis	3	25	2	17	0	-	0	-
Lymphoid Hyperplasia (Gastric)	5	42	10	83	11	92	5	42
<u>Hepatic</u>								
Alkaline PO ₄ Elevation	3	25	2	17	0	-	0	-
Transaminase Elevation	2	17	2	17	0	-	0	-
Bile Duct Hyperplasia	1	8	1	8	0	-	0	-
Pericholangitis	1	8	1	8	0	-	0	-
<u>Other</u>								
Amyloidosis	1	8	0	-	0	-	0	-
Testicular Degeneration	2	17	0	-	0	-	0	-

¹ Computed as days on test/number of days the sign was observed x 100.

TABLE 9: INCIDENCE OF ARTERIOPATHY IN DIFFERENT
TISSUES OF DOGS TREATED WITH HCB
AT 1000 MG/DAY

Number of Treatments	43	79	227	299
Dog Number and Sex	1096F	1077M	1075M	1100F
Adrenal	+			
Esophagus	+		+	
Eye	+			
Heart	+			
Large intestine	+			
Liver	+	+		
Mammary gland	+			
Mediastinum	+			+
Omentum			+	
Ovary				+
Pancreas	+			
Skeletal muscle	+			
Small intestine	+			
Spinal cord	+			
Stomach	+			
Thyroid	+			
Trachea			+	
Tracheal lymph node		+		+
Urinary bladder	+			+

TABLE 10: AVERAGE SERUM FRACTIONS IN DOGS RECEIVING HCB
(ALL VALUES = gm %)

Treatment Group (mg/dog)	Time (wks)	Protein	Albumin	Globulin	A/G (ratio)	α -1	α -2	β -1	β -2	γ
All Dogs	-3	7.29 ±.94	2.85 ±.45	4.45 ±.64	.64 ±.10	1.15 ±.30	.93 ±.20	.90 ±.20	.87 ±.30	.59 ±.20
All Dogs	0	6.10 ±.31	2.62 ±.42	3.47 ±.49	.85 ±.57	.86 ±.30	.77 ±.20	.69 ±.20	.67 ±.20	.47 ±.15
1,000	13	11.3	6.8	4.4	1.60	.93	1.19	1.86	0.10	0.35
	20	7.41	2.40	5.01	.48	.88	1.36	.90	.70	1.14
	39	5.88	3.13	2.75	1.19	.60	.62	.50	.52	.45
	50	6.58	3.98	2.60	1.56	.60	.42	.60	.78	.24
100	13	6.48	4.7	1.8	2.77	.38	.23	.90	.00	.28
	20	7.42	2.69	4.73	.57	.89	1.25	.66	.94	1.02
	39	7.01	3.58	3.40	1.08	.83	.56	.91	.54	.59
	50	7.29	4.11	3.17	1.33	.64	.53	1.03	.54	.41
10	20	7.46	3.10	4.36	.72	.83	1.15	.56	.78	1.03
	39	6.74	4.11	2.63	1.61	.70	.49	.79	.38	.30
	50	7.11	4.88	2.24	2.20	.51	.35	.69	.39	.30
1	13	6.50	4.6	1.95	2.37	.30	.48	.90	.00	.20
	20	7.59	3.16	4.43	.71	.78	1.26	.77	.79	.86
	39	6.68	3.99	2.69	1.49	.84	.38	.80	.29	.38
	50	6.74	4.29	2.46	1.86	.84	.20	.95	.15	.33
0	13	6.4	4.62	1.80	2.78	.40	.50	.70	.28	.37
	20	8.10	3.24	4.86	.68	.90	1.36	.79	.81	.96
	39	6.86	4.59	2.28	2.25	.59	.24	.55	.66	.24
	50	6.95	4.33	2.63	1.70	.60	.36	.96	.34	.31

Table 11: Lymphoid Hyperplasia In The
Gastric Mucosa of Dogs Which
Received HCB.

Dose HCB (mg)	1000	100	10	1	0
Incidence ^a	5/12	10/12	11/12	5/12	0/12
%	42	83	92	42	42

a. Number of animals affected/number of animals evaluated.

absorption, metabolism, biosynthetic pathways, hepatic iron stores and an interaction between HCB and estrogens.

The absorption of HCB by rats has been demonstrated. Albro and Thomas (1974) determined fecal residue following oral administration and showed 82 and 72% absorption for levels of 12 and 30 mg/kg. Other investigators have studied time and dose related bioaccumulation of HCB in various organs and tissues of rats during the course of long term oral administration. Villeneuve (1975) gave male rats HCB in corn oil at 1, 10 and 100 mg/kg/da for 14 days. Liver and fat HCB reached maximum values of 268 and 3,860 ppm, respectively. Avrahami and Gernert (1972) examined the adipose tissue from female rats after 10 wks at various dietary concentrations; dose and adipose tissue levels of HCB correlated and reached 500 ppm in body fat at dietary levels of 50 ppm. Administered HCB in the present canine study may have been incompletely absorbed. However, adipose tissue levels (Table 2) were comparable to those in the rat studies cited. The comparative rates of HCB absorption in dogs and rats is undetermined at this time. However, if body fat concentrations are used as an index of systemic exposure, then enough HCB was absorbed by the dogs in the present study to cause porphyria, since comparable levels in a susceptible species, such as the rat, produce porphyria (Grant, *et. al.*, 1975).

Relative species differences in the response of hepatic mixed function oxidases might offer another explanation for the dissimilar toxicity. The stimulating effect of HCB on the metabolism of foreign chemicals by the rat is established. Turner, *et. al.*, (1974) fed 330 ppm for 10 days and discovered that the activity of the hepatic microsomal hydroxylases, demethylases, esterases and cytochrome P-450, were increased over untreated animals. Independently, Stonard *et. al.*, (1974) carried out similar rat experiments in both sexes and produced the same results. Most recently, Grant, *et. al.*, (1975) performed a multifacet study with HCB in male and female rats whereby three hepatic parameters, concentration of HCB, microsomal activity and porphyrin level, were simultaneously investigated. Hepatic HCB was significantly higher in females, 267 to 200 ppm, but this produced disproportionately elevated hepatic porphyrin, 600 mM compared with 11.5 mM in the male. This

disparity was apparently unrelated to hepatic demethylase or hydroxylase stimulation which were activated in both sexes to the same degree. This work, which awaits confirmation, indicates that the porphyrogenicity of HCB is unrelated to the auto-stimulation of biodegradation in rats. Presumably, the same conclusion could apply to the dog.

An equally relevant question is whether the dog has typical biosynthetic and excretory pathways for porphyrin metabolism which would be responsive to HCB stimulation. Porphyrin synthesis begins with the formation of ALA from succinyl-CoA and glycine, a reaction catalyzed by mitochondrial ALA synthetase (ALAS). Granick and Urata, (1963) have shown that most porphyrogenic chemicals, including HCB, stimulate de novo synthesis of this enzyme, leading to excesses of ALA, the monopyrrole, porphobilinogen, and the tetrapyrroles, uroporphyrin, coproporphyrin, and protoporphyrin. Possibly, the dog excretes surplus ALA without further modification so that the fluorescing aromatic congeners in the liver would remain at normal levels. This hypothesis was tested and unsupported by an analysis of urinary ALA in 3 dogs at 1000 mg/da showing severe toxic reactions. No significant differences were found between these and 3 control dogs.

There are no literature reports describing spontaneous porphyria in dogs, although the condition exists in cattle, squirrels and a strain of cats (Levin, 1975). Chemical porphyria in dogs is a rare occurrence, despite the extensive use of beagles in toxicity testing. Only 2 published accounts describe this condition, in a limited number of dogs, produced by 2 experimental organic compounds. The toxicity of 2-ethyl-2-phenyl-butyramide is reported in an abstract (Zaki, 1973). The second, SC-28034, was used in a study involving 3 beagle dogs, (Stejskal, et. al. 1975). Chronic lead ingestion caused an increase in urinary excretion of coporphyrins, in 1 of 2 dogs (Solomon and Cowgill, 1948).

Taljaard, et. al., (1972) have shown a direct relationship between liver iron and HCB induced porphyria in female Wistar rats. If feeding 0.3% HCB was pre-

ceded by a 14 day pretreatment with injectable iron dextran, then liver porphyrins accumulated more rapidly compared to non-siderotic female rats on the same diet. Iron dextran elevated stainable liver iron and, at the same time, caused a centrolobular red fluorescence before either change occurred in the group receiving HCB alone. This effect has been studied and attributed to iron inhibiting uroporphyrin decarboxylation (Joubert, 1973) and a subsequent bioaccumulation of porphyrin precursors. From the standpoint of the present study, this suggested the possibility that differences in hepatic iron levels might contribute to the variation between rat and dog responses to HCB. Incidentally, the sex related sensitivity of the female rat to HCB induced porphyria might also be explained, since older female rats have higher liver iron than young females or males (Kaldor, 1954; Cook *et al.*, 1973). The available literature offers no clear cut answers. (Table 11).

Recent evidence indicates that estrogens interact synergistically with porphyrogenic chemicals to stimulate ALAS and induce acute porphyria. Ippen, *et al.*, (1972) fed 0.2% HCB to male rats and administered estradiol alone or in combination with progesterone or testosterone to show an enhanced urinary excretion of porphyrins in the animals receiving HCB plus steroidal hormones. This work was corroborated (Grant, *et al.*, 1975) by feeding HCB to castrated male and female rats and mice for varying periods of time and then analyzing liver porphyrins. Hepatic porphyrins in intact females were higher than male counterparts. Moreover, ovariectomy decreased porphyrin accumulation during HCB administration compared with intact females. The work of Weissman, *et al.*, (1974) with two other porphyrogenic chemicals, allylisopropylacetamide and 3,5-dicarbethoxy-1,4-dihydro-2,4,6-trimethylpyridine, showed that either of these agents and pregnanolone increased the activity of ALAS in mice. In addition, pretreatment with a hypocholesterolemic agent prevented ALAS stimulation, an activity which could be restored by including pregnanolone in the regimen.

This information offers the possibility that a relative estrogenic exposure may explain the difference in specie responses to HCB. Plasma estrogens have been measured during estrus in the rat (Butcher, 1974) and dog (Bell, *et al.*, 1971; Jones, *et al.*, 1973; Concannon, 1975) and found to be similar. In both species, estradiol rises from

TABLE 11: IRON CONCENTRATIONS IN DOG AND RAT LIVER

<u>Species</u>	<u>Sex/Age</u>	<u>Total Iron</u> (mg/gm Wet Tissue)	<u>Reference</u>
Dog	Not Reported	0.250	Bogniard and Whipple, 1932
Dog	Not Reported	0.205	Brown, <u>et al.</u> , 1957
Rat	Male/4-18 mo	0.20	Kaldor, 1958
	Female/4 mo	0.37	
	8 mo	0.55	
	18 mo	0.68	
Rat	Male/4 mo	0.13	Gralla, 1975
	Female/4 mo	0.214	

approximately 10-20 pg/ml during metestrus to 60-80 pg/ml at proestrus, a peak which lasts less than 24 hours. However, the rate of repetitive cycling must lead to a wide discrepancy in total exposure to endogenous estrogens. A single complete canine estrus cycle usually requires 6 months while the same series of events in rats occupies 4-5 days. Thus, anestrus, with dormant ovaries and low plasma estrogen, covers 3-5 months in the bitch (Concannon, 1976) and, because of short overlapping cycles, is virtually non-existent in the female rat. Therefore, the female rat may be in a constant state of relative estrogen exposure with an attendant hypersensitivity to HCB, while the female dog is not.

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II. APPENDIX
Individual Animal Data

HEMATOLOGY AND CLINICAL CHEMISTRY BASELINE VALUES FROM MALE AND FEMALE BEAGLE DOGS

Parameter	Males		Females	
	n = 10, E = 39		n = 8, E = 22	
	Mean	Range (p = .05)	Mean	Range (p = .05)
HCT (%)	46.2	39.8 - 52.66	47.5	40.7 - 54.3
HGB (GM %)	15.9	13.0 - 18.7	16.4	13.6 - 19.2
RBC ($\times 10^6/\text{mm}^3$)	6.6	5.5 - 7.8	6.8	5.6 - 7.8
WBC ($\times 10^6/\text{mm}^3$)	10.7	6.1 - 15.2	11.9	6.4 - 17.3
RET (% RBC)	0.76	0 - 1.9	0.58	0 - 1.4
Thrombocytes ($10^3/\text{mm}^3$)	307.7	185 - 430	315.8	193 - 438
Neut. I (%)	0.66	0 - 2.8	0.67	0 - 2.6
Neut. M (%)	63.5	45.8 - 81.1	62.0	44.9 - 79.4
Lymph (%)	32.6	15.3 - 49.9	34.1	15.6 - 52.6
Eosino. (%)	1.8	0 - 6.4	1.3	0 - 5.4
Baso (%)	0.01	0 - 0.25	0	0 - 0
Mono. (%)	1.39	0 - 4.5	1.2	0 - 4.1
BUN (mg%)	13.9	7.3 - 20.5	15.3	8.1 - 22.4
BS (mg%)	102.3	78.9 - 125.7	99.4	78.4 - 120.4
AP (KAU)	3.5	0.4 - 6.6	3.7	0 - 8.7
SGOT (RFU)	24.6	0 - 62	25.9	0 - 94
SGPT (RFU)	22.0	0 - 46	28.9	0 - 98
PT (Sec)	7.9	5.8 - 10.1	7.7	5.8 - 10.7
Bilirubin T (mg%)	0.19	0 - 0.45	0.22	0 - 0.56
Ca (mg%)	10.5	9.4 - 11.6	10.5	9.1 - 12.0
Cl (meq/l)	112.7	105 - 120	113.0	106 - 120
Wgt. (Kg)	9.9	6.5 - 13.3	9.2	6.4 - 12.0

PCO₂ and pH - Not Available

Data was collected between 9/70 and 11/72.

n = Number of animals

E = Number of determinations

ANIMAL ID: D01077
SPECIES: DOG
SEX: MALE
AGE(MO): 10
RX-DATE: 6/10/75
SUPPLIER: MARSHALL

TREATMENT: HCB
DRUG:

LOT: 938872
DAILY DOSE
(MG/KG): 100.000000
(MG/DOG): 1000.00000
SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
VEHICLE: CAPSULE
CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/24 4/22 5/28 6/10
DAY: 21- 0 29 65 78

--HEMATOLOGY--

HCT(%)	44	46	44	49
HGB(GZ)	15.7	16.2	15.8	16.0
RBC(10 ¹⁶ /CMM)	5.74	6.04	6.01	6.30
WBC(10 ¹³ /CMM)	10.46	10.13	12.98	17.47
NEUT,I(ZWBC)	0.0	0.0	1.0	3.0
NEUT,M(ZWBC)	61.0	56.0	73.0	75.0
NEUT,M(10 ¹³)	6.38	5.67	9.48	13.10
LYMPHO(ZWBC)	35.0	28.0	16.0	15.0
LYMPHO(10 ¹³)	3.66	2.84	2.08	2.62
MONO(ZWBC)	2.0	1.0	7.0	7.0
EOSINO(ZWBC)	2.0	15.0	3.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	1.0	0.0	0.0
RET(ZRBC)	0.6	1.1	0.6	0.1
THR(10 ¹⁴ /CMM)	28	21	19	18
PROTIME(SEC)	8.4	10.4	6.9	8.9

--BLOOD CHEM--

BUN(MGZ)	17.0	14.4	21.9	8.3
BS(MGZ)	96	75	77	24
AP(KAU)	5.3	5.1	4.8	31.1
SGOT(RFU/ML)	15	16	11	21
SGPT(RFU/ML)	31	15	16	12
BILI(MGZ)				
CL-(MEQ/L)	120	114	112	102
CA++(MGZ)	10.6	10.4	10.0	8.6
PCO2(MEQ/L)	46.2	0.0	26.0	
PH	7.303		7.362	
PROTEIN(GZ)	6.20	6.30	5.90	
PCO2(MMHG)	23.8	0.0	44.8	

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1077 Necropsy Date: 10 June 1976
 Dose Level (Mg/Day): 1000 Day: 79

Sampling Time (Weeks)	Total					α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin	Albumin/Globulin (Ratio)						
-3	-	-	-	-	-	-	-	-	-	-
0	6.3	2.1	4.2	0.505	1.0	1.0	1.0	0.6	1.1	0.4
13	5.6	2.4	3.2	0.750	0.4	0.4	1.3	1.2	0.0	0.3
20				Died						
39										
50										

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Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile		
42	1,989	5,309

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1077M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>6/10/75</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>3:15 PM</u>
PATHOLOGY NUMBER	<u>75-4223</u>	DATE KILLED	<u>6/10/75</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Moribund</u>
AGE	<u>10 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>79</u>

SUMMARY:

DRUG INDUCED LESIONS

Omentum: +++ subacute serositis, + focal necrosis, ++ focal fibrosis

Tracheal LN: ++ atrophy, ++ focal hilar fibrosis; arterioles, + focal fibrinoid necrosis

Thymus: ++ atrophy

Spleen: ++ atrophy

Ileum: Peyer's patch, + atrophy

Liver: ++ centrilobular fatty change

Colon: ++ lymphoid atrophy

OBSERVATIONS:

Body Cavities and Serosal Surfaces: There is essentially no subcutaneous fat. The omentum is condensed, and drawn together instead of being a free skin.

Omental fat: The omental fat is criss-crossed by fibrous bands. The areas of fibrosis contained both rapidly replicating fibroblasts and in other cases collagen. There are many small blood

vessels which are surrounded by mononuclear inflammatory cells, primarily lymphocytes and plasma cells. The fat has a bubbly mucinous-like appearance. However, the major portion of fat visible in the omentum is normal. On serosal areas is evidence of acute serositis and serosal necrosis. In these areas, the tissue is very eosinophilic and infiltrated with many polymorphonuclear leukocytes and mononuclear cells. In addition, there is a focal hyperplasia of the serosa.

Hemic and Lymphatic System: The capsule of the spleen is wrinkled, the edges are sharp and on section, the lymphoid nodules can not be seen.

Spleen, Thymus, Ileum, Colon: Lymphoid atrophy.

Digestive System: Esophagus, at the junction with the stomach there is a focal irregularly shaped gray lesion in the mucosa approximately 3.8 cm long and 1.6 cm wide. Histologically, there is focal epithelial desquamation in this area.

Liver: In focal areas throughout the liver, there are vacuoles in hepatocytes of variable sizes; some large, some small, some multi-vacuolated. These appear to be fat droplets. In addition, there is a scattered subacute vasculitis, perivascularitis. The inflammatory cells involved are primarily lymphocytes, occasional polymorphonuclear leukocytes and some plasma cells. These cells are both within the walls of vessels and in the adventitia around them. In addition, in a focal area, there is a single granuloma composed of histiocytic cells, some polymorphonuclear leukocytes in the center and fibrosis with mononuclear inflammatory cells around the margin. This granuloma is compatible with visceral larval migrans.

ANIMAL ID: D01096
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/24/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/24 4/22 5/02
 DAY: 20- 0 29 39

--HEMATOLOGY--

HCT(Z)	44	41	39	33
HGB(GZ)	15.3	14.3	12.4	11.0
RBC(10 ⁶ /CMM)	5.46	5.60	5.41	3.10
WBC(10 ³ /CMM)	10.80	9.94	48.33	13.00
NEUT,I(ZWBC)	0.0	0.0	1.0	1.0
NEUT,M(ZWBC)	70.0	52.0	86.0	82.0
NEUT,M(10 ³)	7.56	5.17	41.56	10.66
LYMPHO(ZWBC)	24.0	45.0	8.0	16.0
LYMPHO(10 ³)	2.59	4.47	3.87	2.08
MONO(ZWBC)	5.0	1.0	5.0	1.0
EOSINO(ZWBC)	1.0	2.0	0.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0
RET(ZRBC)	0.6	0.6	1.1	1.4
THR(10 ⁴ /CMM)	49	31	37	20
PROTIME(SEC)	6.9	7.5	6.9	9.9

--BLOOD CHEM--

BUN(MGZ)	12.3	11.5	11.7	8.0
BS(MGZ)	76	64	64	39
AP(KAU)	6.7	5.9	11.8	15.6
SGOT(RFU/ML)	15	15	17	15
SGPT(RFU/ML)	19	12	12	13
BILI(MGZ)				
CL-(MEQ/L)	121	113	115	117
CA++(MGZ)	9.8	10.6	9.4	8.7
PCO2(MEQ/L)	23.0	25.8	18.2	18.0
PH	7.349	7.350	7.198	7.140
PROTEIN(GZ)	6.30	6.40	6.60	6.60
PCO2(MMHG)	40.9	45.2	44.9	50.7

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1096 Necropsy Date: 2 May 1976
 Dose Level (Mg/Day): 1000 Day: 40

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				γ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$
-3	8.2	3.0	5.2	0.571	1.7	1.6	1.0	0.9
0	6.4	1.8	4.6	0.397	0.8	1.3	0.8	1.0
13				Died				
20								
39								
50								

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
289	630

Bile
16

Page

COMPOUND	HCR
DOSE	1000 mg/dog/day
ROUTE	oral

MICROSCOPIC

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1096F</u>	AGE	<u>10 mo</u>
DAY ONE DATE	<u>3/24/75</u>	SEX	<u>Female</u>
COMPOUND	<u>HC8</u>	NECROPSY DATE	<u>5/2/75</u>
DOSE Mg/Da	<u>1,000</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
PATHOLOGY NUMBER	<u>75-3560</u>	PRENECROPSY CONDITION	<u>Moribund</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Fresh</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>43</u>

SUMMARY:

DRUG INDUCED LESIONS

Blood vessels: coronary arteries, mediastinal arteries, gastric arteries, hepatic arteries, intestinal arteries, pancreatic arteries, thyroid arteries, adrenal, mammary gland, urinary bladder, colon, spinal cord, esophagus, optic artery, femoral artery, +++ focal subacute necrotizing vasculitis; perivasculitis; mediastinal artery, ++ organized recanalized thrombus

Spleen: +++ amyloidosis

Mesenteric lymph node: + amyloidosis

Heart: ++ focal subacute myocarditis, right ventricle, +++ focal interstitial fibrosis

Esophagus: + subacute serositis

Meninges: ++ subacute meningitis

Bone marrow: +++ myeloid hyperplasia

OBSERVATIONS:

Heart: (coronary artery and periadventitial area of the large blood vessels at the base of the heart). There is a very pronounced necrotizing vasculitis and perivasculitis affecting branches of the coronary artery and smaller arterioles surrounding the aorta and pulmonary artery. Walls of these vessels are infiltrated by macrophages and polymorphonuclear leukocytes. There is an

eosinophilic coagulum in the wall of some vessels, plus a proliferative process affecting the intima. The inflammatory reaction is very pronounced. Superficial inflammatory cells include lymphocytes and plasma cells. In the focal epicardial fat, there is pronounced subacute inflammation. This inflammation extends into the adjacent myocardium, producing a focal subacute myocarditis. In a focal area of the right ventricle there was pronounced interstitial fibrosis and subacute inflammation.

Stomach: In moderate sized arteries on the serosal surface of the stomach, there is pronounced subacute vasculitis, perivasculitis. The vessels in the affected area show eosinophilic necrosis in the media and a very pronounced subacute inflammatory infiltrate in the periadventitia.

Liver: Focal subacute necrotizing vasculitis and perivasculitis is present, and in addition, a focal acute hepatitis characterized by aggregates of polymorphonuclear leukocytes in the liver sinusoids. In these focal areas the hepatocytes appear to be slightly atrophic, however, no obvious degeneration or necrosis is apparent.

Trachea and adjacent large blood vessels: There is a very pronounced necrotizing vasculitis perivasculitis. In one medium sized artery there is an organized thrombus which has recanalized.

Duodenum and pancreas: In the tissues just outside the serosa of the duodenum, a medium sized artery shows a very pronounced subacute necrotizing arteritis peri-arteritis. In addition, the medium sized arterioles associated with the pancreas show a similar process.

Mesenteric lymph node; granulomatous lymphadenitis: The lymph node is markedly altered by the presence of large numbers of macrophages forming a sheet in the subcapsular area and extending down to the cortical sinuses. In some cases there are multinucleated giant cells in the cortex. Also scattered among these granulomatous inflammatory cells are polymorphonuclear leukocytes. In some areas of the cortex there is a pink homogeneous substance which is amyloid-like. Congo red stain is slightly positive, and green birefringence with polarized light occurs.

MICROSCOPIC NOTES:

Thyroids: 15% parafollicular cells. The medium size arterioles surrounding the thyroids and also in some cases within the thyroids show a very pronounced subacute necrotizing vasculitis, perivasculitis.

Adrenals: Medium sized arterioles in the adventitia of the adrenals show a subacute necrotizing vasculitis, perivasculitis.

Mammary gland: All arterioles in the submucosa show a focal acute necrotizing vasculitis, perivasculitis.

Jejunum: Medium sized arterioles in the mesenteric fat surrounding this portion of the bowel show a subacute necrotizing vasculitis, perivasculitis. The bowel itself is unremarkable.

Thymus; lymphoid atrophy: The pleura surrounding the perithymic fat shows a subacute proliferative pleuritis. Mesothelial cells have proliferated and there are moderate numbers of mononuclear and polymorphonuclear leukocytes in the tissues.

Mediastinal lymph node: Sinusoidal hemorrhage plus subacute vasculitis and perivasculitis affecting medium sized arterioles is present.

Spleen: Lymphoid nodules throughout the spleen are surrounded by macrophages filled with a pink homogeneous-like substance. In some cases, nodules of macrophages containing this pink homogeneous substance can be seen throughout the parenchyma. The material looks like amyloid. Congo red stain is slightly positive and green birefringence occurs with polarized light.

Urinary bladder: Focal submucosal hemorrhages, subacute focal necrotizing vasculitis, perivasculitis affecting arterioles in the wall of the bladder and the tissue surrounding the bladder. In some of these vessels there appear to be organized recanalized thrombi.

Ileum: Focal subacute perivasculitis surrounding a small arteriole in the mesenteric fat.

Colon: In the submucosa there is a pronounced subacute necrotizing vasculitis, perivasculitis affecting medium sized arterioles. The epithelium lining the colon appears to be slightly deficient in the numbers of goblet cells. Scattered capillaries in the mucosa are distended and congested.

Esophagus: On the serosa of the esophagus there is a slight subacute serositis. In this area there are moderate numbers of mononuclear inflammatory cells, mainly macrophages and plasma cells. Vessels in this area show a mild subacute perivasculitis with a similar inflammatory component in the periadventitia. Not every arteriole is so effected.

Spinal cord: Medium sized arterioles in the subdural cavity show a very pronounced subacute necrotizing vasculitis, perivasculitis. In addition, the pia-arachnoid shows a pronounced subacute inflammatory infiltrate. In this area there are also many neocapillaries. Meningitis surrounds the entire spinal cord, however, it is more pronounced in the focal area adjacent to the previously described vasculitis.

Brain: At the base of the cerebrum in the subdural space there is a focal subacute necrotizing vasculitis, perivasculitis. The walls of the medium sized arterioles in this area have been completely destroyed and the entire area is infiltrated by an inflammatory infiltrate composed of macrophages of plasma cells and polymorphonuclear leukocytes. There also appears to be a subacute meningitis affecting the meninges at the base of the brain and focal hemorrhages in the same area. Similar meningeal inflammation is seen in scattered areas all over the surface of the brain. These lesions are also present in the meninges surrounding the cerebellum and the medulla.

Eye: A medium sized artery adjacent to the optic nerve shows a very pronounced subacute perivasculitis.

Femur: A medium sized arteriole in the outside of the periostium shows subacute necrotizing vasculitis. The bone marrow is hypercellular and contains many myeloid precursors and mature cells.

Rib: The bone marrow within the ribs is hypercellular and shows many myeloid precursors and mature cells.

Bone marrow, Zenker's fixed: This marrow sample shows a preponderance of mature polymorphonuclear leukocytes.

ANIMAL ID: D01115
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 6/10/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 VEHICLE: CAPSULE
 CONCENT(MG/ML): 1000.000000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

NO GRADES

DATE: 3/17 3/24 4/22
 DAY: 7- 0 29

--HEMATOLOGY--

HCT(%)	39	42	41
HGB(GZ)	14.8	15.3	15.0
RBC(10 ¹⁶ /CMM)	5.53	5.63	5.82
WBC(10 ¹³ /CMM)	13.97	12.37	12.62
NEUT,I(ZWBC)	0.0	0.0	0.0
NEUT,M(ZWBC)	67.0	51.0	61.0
NEUT,N(10 ¹³)	9.36	6.31	7.70
LYMPHO(ZWBC)	25.0	45.0	27.0
LYMPHO(10 ¹³)	3.49	5.57	3.41
MONO(ZWBC)	1.0	1.0	5.0
EOSINO(ZWBC)	7.0	3.0	7.0
BASO(ZWBC)	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0
RET(ZRBC)	0.6	0.6	0.4
THR(10 ¹⁴ /CMM)	24	18	22
PROTIME(SEC)	7.9	8.4	6.4

--BLOOD CHEM--

BUN(MGZ)	13.8	13.8	14.1
BS(MGZ)	82	85	89
AP(KAU)	5.4	4.0	3.6
SGOT(RFU/ML)	16	15	16
SGPT(RFU/ML)	14	14	17
BILI(MGZ)			
CL-(MEQ/L)	114	116	120
CA++(MGZ)	11.1	10.5	10.2
PCO2(MEQ/L)	22.0	25.8	25.0
PH	7.388	7.409	7.427
PROTEIN(GZ)	5.80	6.10	5.80
PCO2(MMHG)	35.1	39.6	36.8

(All Values = gm%)

Dose Level (Mg/Day): 1000

Day: 79

Tissue HCB (PPM) Level at Necropsy

<u>Bile</u>	<u>Total</u>	<u>Lipid Extract</u>
206	188	-
		<u>Fat</u>

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1115M</u>	NECROPSY DATE	<u>6/10/75</u>
DAY ONE DATE	<u>3/24/75</u>	EUTHANIZED WITH	<u>—</u>
COMPOUND	<u>HC8</u>	HOUR DIED	<u>2:00 AM (?)</u>
DOSE Mg/Da	<u>1,000</u>	DATE DIED	<u>6/10/75</u>
PATHOLOGY NUMBER	<u>75-4222</u>	PRENECROPSY CONDITION	<u>Poor</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Good</u>
AGE	<u>10 mo</u>	POSTMORTEM INTERVAL	<u>8 hrs.</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>2 hrs.</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>79</u>

SUMMARY:

DRUG INDUCED LESIONS:

Thorax: hemothorax (100 cc)

Lungs: +++ focal acute bronchopneumonia, +++ diffuse congestion

Liver: (+) diffuse fatty change, + focal subacute perivascularitis

Mesenteric LN: ++ atrophy and hilar fibrosis

Colonic LN: ++ atrophy

Ileum: Peyer's patches, ++ atrophy, serosal fibrosis

Spleen: + atrophy

OBSERVATIONS:

Respiratory System: The lungs are moderate red-gray color in the apical and cardiac lobes. On the right side some small areas of lighter pink color are raised above the level of the surrounding lung tissue. There are about 2 x 1 sq. cm. in extent. No other gross lesions are present. Microscopically, diffuse congestion and focal subpleural granuloma composed of histiocytic cells

surrounding fibrosis and some mononuclear cells are observed. A second granuloma is also present showing pronounced focal mineralization. In a focal area of another lobe of the lung there is a slight acute pneumonia with a few polymorphonuclear leukocytes exuded into alveolar spaces. In other lobes of the lung a striking acute pneumonia is present with pronounced exudation of polymorphonuclear leukocytes, alveolar edema and severe congestion. Slight acute inflammation is also observed within the bronchial tree.

Digestive System: The liver is discolored throughout its surfaces and dotted with dark red spots about 1-2 mm in diameter. These vary in density giving a fatty streaky appearance to the whole organ. The spleen is of moderate red-gray color, with superimposed bluish-gray scattered areas of variable size over the whole surface of the organ. The mesentery along the whole length of the small intestine is a deep reddish color with the mesenteric veins appearing to be congested with dark blood. The mucosa of the colon shows a streaky red coloring. This coincides with the edges of the longitudinal folds. The content of the stomach consists of a dark black, slimy material very adherent to the gastric mucosa which is of a faint pink color; this slime is not abundant in quantity, totaling about 4 cc. The same dark, slimy material is also found in the duodenum and continued into the jejunum along about half its length. The final portion of the small intestine contains a yellow-gray more solid, sticky material and the mucosa of this portion of the small intestine is marked by patchy, red areas varying from streaks, 2, 3 mm wide to areas of 1 x 2 sq. cm. Microscopically there is moderate post mortem decomposition and lymphoid atrophy. A slight fatty change is noted throughout the liver. There are variable sized, clear vacuoles in hepatocytes in scattered places throughout the liver. In addition, there is a slight subacute perivascularitis characterized by the presence of mononuclear cells around blood vessels in focal areas. In addition, moderate numbers of macrophages were laden with an unidentified green pigment.

ANIMAL ID: D01128
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 8/13/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/24 4/22 6/16 8/13
 DAY: 6- 0 29 84 142

--HEMATOLOGY--

HCT(%)	42	42	39	33	31
HGB(GZ)	15.6	15.0	13.5	11.1	12.8
RBC(10 ¹⁶ /CMM)	5.64	5.44	5.02	4.08	4.23
WBC(10 ¹³ /CMM)	7.93	8.15	9.17	19.76	21.85
NEUT,I(2WBC)	0.0	0.0	0.0	0.0	1.0
NEUT,M(2WBC)	55.0	62.0	55.0	75.0	84.0
NEUT,M(10 ¹³)	4.36	5.05	5.04	14.82	18.35
LYMPHO(2WBC)	40.0	32.0	41.0	23.0	14.0
LYMPHO(10 ¹³)	3.17	2.61	3.76	4.54	3.06
MONO(2WBC)	1.0	1.0	1.0	0.0	1.0
EOSINO(2WBC)	4.0	5.0	3.0	2.0	0.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0
RET(2RBC)	0.5	0.2	0.2	1.1	0.8
THR(10 ¹⁴ /CMM)	30	33	36	60	23
PROTIME(SEC)	9.5	8.9	5.9	6.9	6.9

--BLOOD CHEM--

BUN(MGZ)	16.5	16.3	19.3	13.6	17.2
BS(MGZ)	89	81	86	81	75
AP(KAU)	3.3	2.2	3.1	6.4	5.9
SGOT(RFU/ML)	15	14	81	13	13
SGPT(RFU/ML)	18	13	17	10	10
BILI(MGZ)					
CL-(MEQ/L)	114	113	120	114	113
CA++(MGZ)	9.8	10.0	10.4	9.6	9.0
PCO2(MEQ/L)	24.0	25.8	22.2	20.4	0.0
PH	7.355	7.373	7.403	7.288	
PROTEIN(GZ)	6.60	6.20	6.40		
PCO2(MMHG)	41.9	43.1	34.2	41.2	0.0

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1128 Necropsy Date: 13 August 1975
 Dose Level (Mg/Day): 1000 Day: 143

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.2	2.5	3.7	0.688	1.2	1.0	0.4	0.6	0.5
13	-	-	-	-	-	-	-	-	-
20	8.1	2.5	5.6	0.453	0.9	1.6	1.3	0.8	1.0
39									
50									

Sacrificed

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
621	966

Bile
20

URINALYSIS

ANIMAL NUMBER . . .	(A/3-10)	D1128F
DAY ONE DATE . . .		032475
INITIAL BODY WEIGHT . . .		6.5 Kg
FINAL BODY WEIGHT . . .		5.19 Kg

COMPOUND	•	•	•	•	HCB
DOSE	•	•	•	•	1,000 mg/dog/day
ROUTE	•	•	•	•	oral

Treatment Date	A(UA/11-16)	04227506	197508	1375
Day in Study	I(AU/17-19)	30	88	143
Sp. Gr.	R(U1/20-24)	1.035	1.045	1.065
pH	R(U1/25-29)	6	6	6
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	trace	1+	trace

MICROSCOPIC				
Triple Phosphates	I(U2/20-24)			
Uric Acid	I(U2/25-29)			
Calcium Salts	I(U2/30-34)			
Other	A(U2/35-39)			
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	gran.	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0	0-3	0-1
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)	0-2	0-5	3-7
Mucous	I(U2/60-69)			
Appearance	I(U2/70-80)	yellow	y b	dk. y

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1128</u>	NECROPSY DATE	<u>8/13/75</u>
DAY ONE DATE	<u>3/24/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:25 AM</u>
DOSE Mg/Da	<u>1,000</u>	DATE DIED	<u>8/13/75</u>
PATHOLOGY NUMBER	<u>75-5946</u>	PRENECROPSY CONDITION	<u>Poor</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>9 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>143</u>

SUMMARY:

DRUG INDUCED LESIONS

Visceral peritoneum: stomach, urinary bladder etc., ++ focal subacute serositis, duodenum, pancreas, colon, ++ focal fibrosis

Omentum: ++ focal fibrosis, + focal subacute steatitis

Skin: face, eyelids, +++ acute cellulitis

Mandibular lymph node: ++ subacute lymphadenitis, pericapsular fibrosis

Abdomen: ascites 35 cc

OBSERVATIONS:

General Examination: The skin immediately adjacent to the medial canthus of the eye is denuded. There is a heavy exudate adherent to the hair around the face. There are additional areas of alopecia around the tuber ischii approximately 2 cm in diameter. This skin in this area is scaly and dry. The hair around the margin of the eyelid is denuded. The interdigital area on each foot is slightly swollen. There is essentially no subcutaneous fat. There are approximately 32 cc's of slightly amber, slightly cloudy fluid in the abdominal cavity.

Digestive System: The pancreas is adherent to the lesser curvature of the stomach. The content of the small bowel is a watery semiformed brown material. The stomach contains a large quantity of ingesta. The mucosa of the bowel is essentially unremarkable except for what appears to be folds along its length which may have resulted from the fibrous adhesions of the serosal surface. A short section of the ileum approximately 7 cm, shows a very red mucosa. The bowel particularly in the region of the duodenum and jejunum seems to be slightly thickened. The ileum is a more normal thickness. In the mucosa of the caecum there are focal grey-tan areas approximately 3-4 mm in length and 2 mm in width. The right ovary contains a small quantity of red tinged fluid in the bursal sac. The left ovary was lost and the left horn of the uterus was lost when the adherent mass of the bowel was removed. The texture of the liver is friable. The colon and sections of the small bowel are adherent to each other by firm fibrous adhesions. The adherent bowel forms a large mass at the base of the mesentery which is consolidated by fibrous adhesions. Included in the mass of adhesions is a large area along the lesser curvature of the stomach. Photographs of these adhesions along with the photograph of the face were taken. Mesenteric fat is consolidated into a small mass about 6 x 5 x 2 cm attached to the lesser curvature of the stomach.

Stomach: On the serosal surface of the stomach there is a focal serositis. In the affected area the serosa is hyperplastic and thrown up into a cuboidal-columnar type epithelium. The serosal cells have high nuclear/cytoplasmic ratios. Further along the serosa there is a very marked fibrous reaction exterior to the muscularis externa. In the affected area there is a large quantity of newly laid down collagen and many fibroblasts. In addition, some of the omental fat adherent to the stomach shows very marked fibrosis which is focal and diffuse in character. In one area there is a very large fibrotic nodule.

Duodenum: On the serosal surface of the duodenum there is a very pronounced focal fibrous reaction. External to the outer most muscular layer and apparently external to the serosa itself there were many collagen bundles and mature fibroblasts laid down. The lesion affects approximately 80% of the circumference of the duodenum. The mucosa of the duodenum is unremarkable except for a mild p.m. change.

Mesenteric lymph node: The degree of cellularity of the nodes is normal. Several large subcapsular

granulomas composed predominately of macrophages are present. The central area of these granulomas contains moderate numbers of polymorphonuclear leukocytes. The lesions would appear to arise from parasitic migration.

Jejunum: A piece of mesentery attached to the jejunum shows pronounced focal fibrosis. New collagen and fibroblasts are present. Within this area there is a fine sprinkling of mononuclear inflammatory cells primarily lymphocytes and a rare polymorphonuclear leukocyte.

Urinary bladder: On the serosal surface of the urinary bladder there is a very pronounced focal fibrous reaction with large quantities of collagen and mature fibroblasts being laid down. There is a sprinkling of mononuclear inflammatory cells dispersed throughout the fibrous reaction.

Mandibular lymph node: The node shows considerable polymorphonuclear leukocytes in the pericapsular tissue and the subcapsular sinus producing a mild acute lymphadenitis. This may be related to the ulcerative lesions on the face. In another section the lesion is quite severe with pericapsular fibrosis.

Mesenteric fat: Around the periphery of the mesenteric fat there is a very pronounced fibrous reaction. Large bundles of collagen and new fibroblasts are being deposited. Admixed in the area are moderate numbers of mononuclear cells and a rare polymorphonuclear leukocyte.

Colon: Similarly on the serosal surface of the colon there is a very pronounced focal fibrous reaction.

ANIMAL ID: D01107
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 6/19/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT: 938872
 DAILY DOSE
 (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/06 3/24 4/22 6/16
 DAY: 18- 0 29 84

--HEMATOLOGY--

HCT(Z)	46	45	45	48
HGB(GZ)	16.5	15.8	15.9	14.9
RBC(10 ¹⁶ /CMM)	6.55	6.46	6.34	7.03
WBC(10 ¹³ /CMM)	12.78	15.27	14.70	11.01
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	57.0	68.0	68.0	74.0
NEUT,M(10 ¹³)	7.28	10.38	10.00	8.15
LYMPHO(ZWBC)	36.0	17.0	24.0	24.0
LYMPHO(10 ¹³)	4.60	2.60	3.53	2.64
MONO(ZWBC)	2.0	5.0	3.0	2.0
EOSINO(ZWBC)	5.0	10.0	5.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0
RET(ZRBC)	0.9	0.9	0.6	0.1
THR(10 ¹⁴ /CMM)	38	36	25	19
PROTIME(SEC)	6.9	7.9	5.9	6.9

--BLOOD CHEM--

BUN(MGZ)	18.5	19.6	21.3	9.4
BS(MGZ)	82	85	80	44
AP(KAU)	3.6	3.6	4.8	9.5
SGOT(RFU/ML)	19	17	21	36
SGPT(RFU/ML)	21	15	19	25
BILI(MGZ)				
CL-(MEQ/L)	112	115	118	97
CA++(MGZ)	9.8	10.2	11.0	8.3
PCO2(MEQ/L)	0.0	25.0	23.8	23.2
PH		7.387	7.412	7.356
PROTEIN(GZ)	7.00	6.50	6.20	6.20
PCO2(MMHG)	0.0	40.2	36.3	40.2

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1107 Necropsy Date: 19 June 1976
 Dose Level (Mg/Day): 1000 Day: 88

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	7.0	2.5	4.5	0.540	1.0	0.8	0.9	1.0	0.8
0	6.5	2.0	4.5	0.430	1.0	1.2	0.8	0.8	0.7
13	6.0	3.9	2.1	1.900	0.3	0.6	0.9	0.0	0.2
20				Died					
39									
50									

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
76	1,704	2,545

URINALYSIS

ANIMAL NUMBER (A/3-10) D1107M
 DAY ONE DATE 032475
 INITIAL BODY WEIGHT 9.8 Kg
 FINAL BODY WEIGHT 5.68 Kg

COMPOUND HCB
 DOSE 1000 mg/dog/day
 ROUTE oral

Treatment Date	AIAU/11-16	042275	061975
Day in Study	IUAU/17-19	29	87
Sp. Gr.	RIU1/20-24	1.054	1.040
pH	RIU1/25-29	6	6
Sugar	IUI1/30-34	0	0
Ketones	IUI1/35-39	0	1ge
Blood	IUI1/40-44	0	0
Protein	IUI1/45-49	trace	1+
REAGENT STRIP			
MICROSCOPIC			
Triple Phosphates	I(U2/20-24)		
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)		
Other	A(U2/35-39)		
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	gran.	sperm
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-3	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-2	0-2
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-5	0-2
Mucous	I(U2/60-69)		
Appearance	I(U2/70-80)	yellow	yb

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1107M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/24/75</u>	NECROPSY DATE	<u>6/19/75</u>
COMPOUND	<u>HBC</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR KILLED	<u>3:30 PM</u>
PATHOLOGY NUMBER	<u>75-4483</u>	DATE KILLED	<u>6/19/75</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Moribund</u>
AGE	<u>10 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>88</u>

SUMMARY:

DRUG INDUCED LESIONS

Lungs: ++ focal acute bronchiopneumonia

Liver: ++ centrilobular fatty change

Omental fat: + focal subacute perivascularitis

Adrenals ++ focal subacute adrenalitis

Duodenum: serosa, + focal proliferative serositis

Cecum: serosa, + focal fibrosis

Urinary bladder: + focal subserosal fibrosis and hemorrhages

Spleen: - lymphoid atrophy

Testes: + focal degeneration

Epididymis: ++ focal epithelial degeneration

Colon: + focal mucosal hemorrhages

OBSERVATIONS:

Respiratory System: The left apical lobe has a mottled gray appearance affecting approximately 30% of the surface, particularly on the medial surface. The left cardiac lobe has a sharply demarcated gray area affecting approximately 60% of the surface. The right apical and cardiac lobes are essentially unremarkable. The intermediate right lobe is small, gray-tan and firm. The right diaphragmatic lobe has focal areas of firmness throughout. Microscopically, several lobes show a pronounced focal acute bronchopneumonia. There are many polymorphonuclear leukocytes within small bronchioles and also in the adjacent alveoli. One lobe, in addition to showing a focal acute pneumonia, also shows evidence of more chronic interstitial fibrosis.

Digestive System: The various loops of the small intestine are adherent to each other and also to the mesentery by fine fibrinous adhesions, the omental fat seems to be gathered together and folded on itself. In the pyloric region there are multiple focal punctate, black, and slightly linear lesions approximately 25-30. These probably represent focal erosions with slight mucosal bleeding. The mucosa of the small and large intestine has a patchy redness, the small intestine is filled with a bile and mucoid-like substance. The large intestine contains a very small quantity of a pasty fecal material. Visible along the lesser curvature of the stomach are multiple small focal erosions up to 3 mm in diameter. The liver has a slight yellow tinge.

MICROSCOPIC OBSERVATIONS:

Omental fat: Focal subacute perivascularitis. Around small arterioles within the fat there are small to moderate numbers of mononuclear cells.

Cecum: Along the serosal surface of the cecum there is a slight fibrous thickening in focal areas. The mucosa shows very slight focal hemorrhages. The luminal surface shows moderate post mortem decomposition.

Duodenum: The mucosa along the luminal surface shows moderate post mortem decomposition. Capillaries on this surface are also congested. There are a few crypt abscesses. In the serosal surface there appears to be a slight proliferative serositis. In the affected areas there

is fibrosis and slight neocapillary formation. In addition, there are a few mononuclear cells in the fibrotic tissue. Lymphoid tissue in the submucosa appears to be slightly atrophic.

Ileum: Along a focal segment of the serosa there is marked fibrosis and slight focal hemorrhage. The lesion appears to represent a healing phase of a proliferative serositis.

Liver: This organ shows centrilobular fatty changes. Hepatocytes surrounding central veins contain both large and small clear vacuoles. Some of these vacuoles contain a fine fibrillar pink material.

Testes: Moderate numbers of segments of the seminiferous tubules contain incompletely matured spermatogonia. Mature spermatids are visible in some segments of the seminiferous tubules. In some segments of the epididymis there are vacuoles in the columnar epithelium lining the epididymis. Within these vacuoles there are pyknotic nuclei and apparently cellular debris. Within the lumen of the epididymal tubules there are mature spermatids and immature spermatogonia along with the slight degeneration in the testes.

Urinary bladder: In the subserosal area of the bladder there is a pronounced fibrosis. Within the fibrotic tissue there is focal hemorrhages.

ANIMAL ID: D01070
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 12
 RX-DATE: 3/24/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/24 4/22 6/16 8/13 12/11 3/09
 DAY: 21- 0 29 84 142 262 351

--HEMATOLOGY--

HCT(X)	44	48	47	46	43	48	38
HGB(GX)	16.4	16.9	16.6	15.6	13.6	17.4	13.1
RBC(10 ¹⁶ /CMH)	5.48	6.79	6.65	5.64	5.62	6.88	5.39
WBC(10 ¹³ /CMH)	7.10	7.52	8.90	6.01	10.92	13.83	11.21
NEUT,I(XWBC)	0.0	0.0	0.0	0.0	0.0	6.0	3.0
NEUT,M(XWBC)	65.0	50.0	58.0	33.0	68.0	66.0	46.0
NEUT,H(10 ¹³)	4.62	3.76	5.16	1.98	7.43	9.13	5.16
LYMPHO(XWBC)	25.0	38.0	33.0	55.0	25.0	24.0	44.0
LYMPHO(10 ¹³)	1.78	2.86	2.94	3.31	2.73	3.32	4.93
MONO(XWBC)	2.0	3.0	4.0	1.0	3.0	0.0	2.0
EOSINO(XWBC)	8.0	9.0	5.0	11.0	4.0	4.0	5.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	0.5	0.6	0.2	0.5	0.8	0.8	0.1
THR(10 ¹⁴ /CMH)	22	25	21	17	40	29	21
PROTIME(SEC)	7.9	10.9	15.4	10.5	6.9	8.4	7.4

--BLOOD CHEM--

BS(MGX)	86	78	75	86	88	68	68
AP(KAU)	3.0	3.9	4.4	3.6	5.9	4.6	3.9
SGOT(RFU/ML)	14	15	17	13	10	10	14
SGPT(RFU/ML)	18	13	15	10	9	7	9
BILI(MGX)	116	114	114	112	106	114	113
CL-(MEQ/L)	10.0	10.2	10.2	10.2	10.2	10.4	10.2
CA++(MGX)	24.0	26.4	25.8	23.2	27.2	28.4	26.0
PCO2(MEQ/L)	7.358	7.405	7.364	7.395	7.325	7.439	7.344
PH	5.90	5.90	6.20	36.8	51.3	41.1	6.00
PROTEIN(GX)	41.2	41.1	43.9	36.8	51.3	41.1	46.4
PCO2(MMHG)							

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1070 Necropsy Date: 14 April 1976
 Dose Level (Mg/Day): 1000 Day: 385

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	7.5	3.1	4.4	0.703	1.3	0.9	1.1	0.7	0.5
0	5.9	2.3	3.6	0.639	1.0	0.8	0.7	0.6	0.6
13	-	-	-	-	-	-	-	-	-
20	7.6	2.6	5.0	0.510	1.0	1.2	0.9	0.8	1.1
39	6.6	4.1	2.5	1.659	0.5	0.6	0.5	0.7	0.2
50	6.9	4.7	2.2	2.068	0.8	0.0	0.6	0.6	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
822	1,050

Bile
20.9

URINALYSIS

ANIMAL NUMBER (A/3-10) D1070F
DAY ONE DATE 032475
INITIAL BODY WEIGHT 6.3 Kg
FINAL BODY WEIGHT

COMPOUND HCB
DOSE 1000 mg/dog/day
ROUTE oral

Treatment Date	A1A/11-16	042275	062075	081375	121275	030976
Day in Study	IIU1/17-19	30	89	143	264	352
Sp. Gr.	RIU1/20-24	1.700	1.055	1.070	1.056	1.058
pH	RIU1/25-29	8	7	6	6.5	6.5
Sugar	IIU1/30-34	0	0	0	0	0
Ketones	IIU1/35-39	0	0	0	0	0
Blood	IIU1/40-44	0	0	0	0	1+
Protein	IIU1/45-49	trace	1+	trace	1+	trace

REAGENT STRIP	11U2/20-24	11U2/25-29	11U2/30-34	11U2/35-39	11U2/40-44	11U2/45-49
Triple Phosphates						
Uric Acid						
Calcium Salts						
Other						
Cast/LPF 100X (Avg/Field)						
RBC/HPF 400X (Avg/Field)						
WBC/HPF 400X (Avg/Field)						
EP1TH/HPF 400X (Avg/Field)						
Mucous						
Appearance						

Microscopic	11U2/20-24	11U2/25-29	11U2/30-34	11U2/35-39	11U2/40-44	11U2/45-49
Triple Phosphates						
Uric Acid						
Calcium Salts						
Other						
Cast/LPF 100X (Avg/Field)						
RBC/HPF 400X (Avg/Field)						
WBC/HPF 400X (Avg/Field)						
EP1TH/HPF 400X (Avg/Field)						
Mucous						
Appearance						

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1070F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>4/14/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>10:00</u>
PATHOLOGY NUMBER	<u>76-2568</u>	DATE KILLED	<u>4/14/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Fair</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>385</u>

SUMMARY:

DRUG INDUCED LESIONS

Peritoneum (omentum, liver, stomach, jejunum, colon, cecum): + focal fibrous adhesions
Stomach, fundus, body-pyloric antrum: +++ lymphoid hyperplasia

OBSERVATIONS:

General Examination: The body is that of a female beagle in fair condition. The hair coat is dry and slightly scurfy. Epiphora is evident by the marked moisture near the medial canthus of each eye.

Body Cavities and Serosal Surfaces: Moderate numbers of firm fibrous adhesions are present between omentum, gastrointestinal tract and liver. The omentum is condensed in size and adherent to itself.

Digestive System: The entire gastric mucosa in the fundus and pyloric antrum is studded with closely arranged nodules approximately 1.5 to 2 mm in diameter. There is slight extension into the adjacent body of the stomach. In the fundic region there are about 200 nodules and in the pyloric antrum about 150.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the gastric mucosa are numerous small and large, sometimes confluent lymphoid nodules. These nodules are present in both the body-pyloric antrum area and in the fundic region.

Colon: Focal areas of fibrosis are present in the mesentery attached to the colon.

ANIMAL ID: D01075
SPECIES: DOG
SEX: MALE
AGE(MO): 9
RX-DATE: 3/24/75
SUPPLIER: MARSHALL

TREATMENT: HCB
LOT: 938872
DAILY DOSE (MG/KG): 100.00000
(MG/DOG): 1000.00000
SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
FORMULATION VEHICLE: CAPSULE
CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/24 4/22 6/16 8/13
DAY: 21- 0 29 84 142

--HEMATOLOGY--

HCT(Z)	45	46	47	45	47
HGB(GZ)	16.1	15.6	16.6	15.0	14.2
RBC(10 ¹⁶ /CHM)	6.20	6.41	6.44	8.15	6.08
WBC(10 ¹³ /CHM)	11.45	11.07	13.54	20.84	27.86
NEUT,I(ZWBC)	0.0	0.0	2.0		5.0
NEUT,M(ZWBC)	68.0	55.0	63.0	69.0	79.0
NEUT,H(10 ¹³)	7.79	6.09	8.53	14.38	22.01
LYMPHO(ZWBC)	32.0	40.0	26.0	30.0	9.0
LYMPHO(10 ¹³)	3.66	4.43	3.52	6.25	2.51
MONO(ZWBC)	0.0	1.0	7.0	0.0	4.0
EOSINO(ZWBC)	0.0	4.0	2.0	1.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.0	0.7	1.8	0.6	1.4
THR(10 ¹⁴ /CHM)	31	18	33	16	21
PROTINE(SEC)	7.9	8.9	7.4	9.4	6.5

--BLOOD CHEM--

BUN(MGZ)	15.6	14.0	16.6	14.9	12.3
BS(MGZ)	101	96	93	82	75
AP(KAU)	4.3	4.1	3.9	3.0	3.0
SGOT(RFU/ML)	13	16	14	12	7
SGPT(RFU/ML)	12	13	15	11	9
BILI(MGZ)					
CL-(MEQ/L)	115	113	117	111	110
CA++(MGZ)	9.8	10.2	11.0	9.6	9.8
PCO2(MEQ/L)	24.2	26.5	26.2	20.0	24.5
PH	7.298	7.370	7.392	7.342	7.256
PROTEIN(GZ)	6.20	5.80	5.70		
PCO2(MMHG)	48.2	44.9	42.1	35.3	53.9

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1075 Necropsy Date: 5 November 1975
 Dose Level (Mg/Day): 1000 Day: 227

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$
-3	7.8	3.5	4.3	0.802	1.0	1.0	1.0	1.0
0	5.8	2.3	3.5	0.644	0.9	0.7	0.4	0.9
13	13.8	7.8	6.0	1.314	1.1	1.9	1.8	0.8
20	7.3	2.1	5.2	0.404	0.8	1.4	1.0	0.8
39				Died				
50								

1
8
1

Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	50	
	1,062	1,792

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URINALYSIS

ANIMAL NUMBER (A/3-10) D1075 M
DAY ONE DATE 032475
INITIAL BODY WEIGHT 8.8 Kg
FINAL BODY WEIGHT

COMPOUND HCB
DOSE 1000 mg/dog/day
ROUTE oral

Treatment Date	A1A/11-16	042275	061975	081375
Day in Study	11A/17-19	30	88	143
Sp. Gr.	11U1/20-24	1.066	1.022	1.055
pH	11U1/25-29	8	6	6
Sugar	11U1/30-34	0	0	0
Ketones	11U1/35-39	0	0	0
Blood	11U1/40-44	0	0	0
Protein	11U1/45-49	2+	0	1+
REAGENT STRIP				
MICROSCOPIC				
Triple Phosphates	11U2/20-24	+		
Uric Acid	11U2/25-29			
Calcium Salts	11U2/30-34			1+
Other	11U2/35-39			
Casts/LPF 100X (Avg/Field)	11U2/40-44	gran.		blood
RBC/HPF 400X (Avg/Field)	11U2/45-49	0-2	0	0
WBC/HPF 400X (Avg/Field)	11U2/50-54	0-4	0	0-3
EPITH/HPF 400X (Avg/Field)	11U2/55-59	0-5	2-7	0-2
Mucous	11U2/60-64			
Appearance	11U2/65-69	yellow	lt. y	yb

• Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1075M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>11/5/75</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>9:40</u>
PATHOLOGY NUMBER	<u>75-7617</u>	DATE KILLED	<u>11/5/75</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Died</u>
AGE	<u>1 yr.</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>227</u>

SUMMARY:

DRUG INDUCED LESIONS

Arterioles, esophagus, trachea, omentum: ++ fibrinoid necrosis

Tracheal artery: ++ subacute perivascularitis

Esophagus: +++ periesophageal granulomatous inflammation

Trachea: +++ peritracheal abscess

Tracheal lymph node, capsule: ++ focal granulomatous inflammation

Omental fat: ++ focal fibrosis ++ focal granulomatous inflammation

Colon: ++ focal chronic serositis

Brain, meninges: + focal subacute meningitis

Testes: (±) degeneration

Lymphoid tissues, Peyer's patches, spleen, thymus: + to ++ atrophy

Heart, coronary fat: (±) focal subacute steatitis

OBSERVATIONS:

General Examination: The body is that of an emaciated male beagle in very poor condition with a dry scurfy coat. A shiny ocular discharge is matted on the face at the medial canthus

of each eye. A 2 cm² decubital pore is present on the lateral surface of the right hock.

Body Cavities and Serosal Surfaces: The abdomen contains 10 cc of pale straw colored fluid. The omentum is condensed and the quantity of fat very reduced. A few fibrous adhesions are present between the serosa of the intestines and the mesentery.

Hemic and Lymphatic System: The spleen is smaller than normal.

MICROSCOPIC OBSERVATIONS:

Stomach: Within the lamina propria a few small aggregates of lymphocytes are present. In the gross these did not appear as nodules in the mucosa of the stomach.

Heart: The coronary fat shows some evidence of subacute inflammation with small aggregates of polymorphonuclear leukocytes and mononuclear cells including lymphocytes and plasma cells being present.

Liver: In the parenchyma of the liver are scattered focal macrophages RE cells containing a light green pigment. These RE cells are quite rare.

Trachea: Peri-tracheal tissue shows a very severe focal area of acute inflammation. This looks like an abscess. There are numerous polymorphonuclear leukocytes and macrophages in the area.

Tracheal lymph node: In the pericapsular area there is a pronounced ++ focal granulomatous inflammation with numerous macrophages. The node itself shows moderate amount of hemorrhage in the medullary sinuses. There is considerable fibrosis at the hilum of the node. Small arterioles in the periadventitia around the node show pronounced fibrinoid necrosis. The wall of this arterioles is completely hyalinized and infiltrated by necrotic inflammatory cells. The periadventitia around the vessel contains numerous lymphocytes and plasma cells.

Mesenteric lymph node: Scattered about within the parenchyma of the mesenteric lymph node are focal areas of granulomatous inflammation.

Omental fat: The omental fat shows extensive fibrosis and granulomatous inflammation. Arterioles within the fat show a very severe hyalinization. In some cases the walls appear to be

completely necrotic. There are numerous polymorphonuclear leukocytes and macrophages in the peri-adventitia. In one case a small arteriole within a nerve shows marked subacute perivasculitis.

Thymus: ++ atrophy.

Testes and epididymis: The epididymis contain moderate numbers of mature sperm and numerous spermatogenic giant cells and spermatogonia. Seminiferous tubules show moderate evidence of degeneration. There are numerous spermatogenic giant cells and an incomplete compliment of spermatogonia in the various tubules. The opposite testicle shows a fairly large number of spermatotids in the seminiferous tubules. An occasional multinucleated abnormal spermatogonia is observed. Overall the degree of testicular degeneration is slight.

Ileum: Lymphoid nodules in the submucosa appear to be slightly less cellular than normal.

Spleen: Lymphoid nodules in the spleen appear to be slightly less cellular than normal.

Esophagus: The serosal surface of the esophagus shows a pronounced +++ granulomatous inflammation. This appears to be oriented around arterioles. The wall of these arterioles is necrotic in some cases. The granulomatous areas of inflammation contain large numbers of macrophages and numerous polymorphonuclear leukocytes. The wall in the subintimal area of one arteriole appears to be hyalinized.

Colon: On the serosal surface of the colon there were numerous focal areas of thickening and fibrosis.

Brain: In a focal area of the meninges surrounding the brain there is a pronounced subacute inflammation consisting of plasma cells and polymorphonuclear leukocytes.

ANIMAL ID: D01089
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/24/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/24	4/22	6/16	8/13	12/11	3/09
DAY:	20-	0	29	84	142	262	351
--HEMATOLOGY--							
HCT(Z)	39	40	39	42	41	48	39
HGB(GZ)	14.2	14.3	14.3	15.1	14.2	16.2	13.2
RBC(10 ¹⁶ /CMH)	4.67	5.59	5.65	5.37	5.58	5.02	5.09
WBC(10 ¹³ /CMH)	10.07	9.05	11.16	11.37	13.19	16.02	16.67
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	2.0	7.0	0.0
NEUT,M(ZWBC)	70.0	55.0	61.0	58.0	67.0	59.0	62.0
NEUT,H(10 ¹³)	7.05	4.98	6.81	6.59	8.84	9.45	10.34
LYMPHO(ZWBC)	28.0	34.0	32.0	35.0	25.0	31.0	32.0
LYMPHO(10 ¹³)	2.82	3.08	3.57	3.98	3.30	4.97	5.33
MONO(ZWBC)	1.0	0.0	0.0	0.0	1.0	0.0	1.0
EOSINO(ZWBC)	1.0	11.0	7.0	7.0	5.0	3.0	5.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.4	0.5	0.3	0.5	0.8	1.9	0.9
THR(10 ¹⁴ /CMH)	31	28	39	33	11	27	35
PROTIME(SEC)	7.4	8.5	7.4	8.9	6.9	8.4	7.4

--BLOOD CHEM--

BUN(MGZ)	16.2	17.2	19.7	13.6	17.4	13.5	12.9
BS(MGZ)	84	77	77	75	94	70	73
AP(KAU)	3.0	2.9	2.1	3.6	4.1	2.8	2.9
SGOT(RFU/ML)	15	17	13	13	11	11	15
SGPT(RFU/ML)	19	15	17	10	8	5	8
BILI(MGZ)							
CL-(MEQ/L)	117	112	114	112	113	113	116
CA++(MGZ)	9.6	10.0	9.8	10.0	9.6	9.4	9.1
PCO2(MEQ/L)	23.2	25.0	23.8	20.2	25.8	26.0	23.0
PH	7.307	7.373	7.352	7.354	7.290	7.394	7.336
PROTEIN(GZ)	6.00	6.00	5.80				6.00
PCO2(MMHG)	45.2	42.0	41.4	35.0	52.0	41.3	41.8

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1089 Necropsy Date: 15 April 1976
 Dose Level (Mg/Day): 1000 Day: 389

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	10.0	4.0	6.0	0.670	1.5	1.1	1.2	1.6	0.6
0	6.0	2.4	3.6	0.651	0.8	1.0	0.5	0.8	0.6
13	13.2	7.5	5.7	1.306	0.7	1.8	2.6	0.0	0.7
20	7.6	2.4	5.2	0.475	0.9	1.3	0.9	0.7	1.4
39	6.5	3.1	3.4	0.926	0.7	0.9	0.5	0.5	0.6
50	6.5	3.5	3.0	1.191	0.2	0.6	0.8	1.3	0.1

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
583	2,100	3,130

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D 1089/M	COMPOUND	HC B
DAY ONE DATE		032475	DOSE	. 1000 mg/dog/day
INITIAL BODY WEIGHT		7.8 Kg	ROUTE	. oral
FINAL BODY WEIGHT				

Treatment Date		A(AU/11-16)	042475	061975	081375	121275	3030976
Day in Study	I(AU/17-19)	32	88	143	264	352	
Sp. Gr.	R(U1/20-24)	1.066	1.050	1.055	1.072	1.054	
pH	R(U1/25-29)	6	7	6	6	6	
Sugar	I(U1/30-34)	0	0	0	0	0	
Ketones	I(U1/35-38)	0	0	0	0	0	
Blood	I(U1/40-44)	0	0	0	0	0	
Protein	I(U1/45-49)	1+	1+	1+	1+	trace	

REAGENT STRIP

Triple Phosphates		I(U2/20-24)	light	4+																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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*** Too numerous to count**

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1089M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>4/15/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>10:30 AM</u>
PATHOLOGY NUMBER	<u>76-2570</u>	DATE KILLED	<u>4/15/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Fair</u>
AGE	<u>23 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>389</u>

SUMMARY:

DRUG INDUCED LESIONS

Omentum, visceral peritoneum (stomach, mesentery, ileocolic junction): +++ fibrous adhesions

OBSERVATIONS:

General Examination: The body is that of a thin male beagle in poor condition with a dry hair coat and focal areas of alopecia scattered over the trunk and perianal area. The face is moist and the skin near the medial canthus of each eye is matted with a sticky gray-brown substance.

Body Cavities and Serosal Surfaces: The abdominal cavity contains approximately 3 cc of red fluid. The surface area of the omentum is reduced to about 4 x 15 cm and it has a firmer texture with complete loss of the normal lacy appearance. The shape of the stomach is very distorted because of diffuse fibrous adhesions between the mesentery and omentum. There is a 2 cm adhesion between the omentum and ileocolic junction.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible on the serosal surface of the stomach and effecting about 25% of the circumference is pronounced fibrosis with numerous fibroblasts, collagen and some hemosiderin laden macrophages. Visible in the mucosa are numerous small and medium sized lymphoid nodules. These were not grossly visible.

Omentum: Bands of fibrous tissue are traversing through the omentum and around the margins. The omentum is adherent to itself. A large amount of the omentum contains the normal complement of fat. The most striking feature is the presence of fibrous bands throughout the structure.

Prostate: Acinar structures immediately surrounding the prostatic urethra appear to be moderately atrophic. Those acinar structures farther out are unremarkable. Among several control prostates one shows a similar change but not as pronounced and the other does not show this change.

ANIMAL ID: D01100
SPECIES: DOG
SEX: FEMALE
AGE(MO): 9
RX-DATE: 3/24/75
SUPPLIER: MARSHALL

TREATMENT: HCB
DRUG: HCB
LOT: 938872
DAILY DOSE
(MG/KG): 100.000000
(MG/DOG): 1000.00000
SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
VEHICLE: CAPSULE
CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/24	4/22	5/28	6/10	6/16	8/13	12/11	1/16
DAY:	18-	0	29	65	79	84	142	262	298

--HEMATOLOGY--

HCT(%)	43	47	45	40	42	41	46	41	41
HGB(GZ)	15.9	16.8	17.1	13.9	13.7	14.0	13.9	13.7	13.7
RBC(10 ¹⁶ /CMH)	5.59	6.40	6.13	5.58	5.81	5.50	5.53	5.53	5.53
WBC(10 ¹³ /CMH)	9.99	8.55	9.13	12.35	8.43	14.11	20.65	46.30	46.30
NEUT,I(XWBC)	0.0	0.0	0.0	0.0	0.0	3.0	0.0	7.0	7.0
NEUT,M(XWBC)	68.0	57.0	58.0	62.0	36.0	65.0	65.0	81.0	81.0
NEUT,M(10 ¹³)	6.79	4.87	5.30	7.26	3.03	9.17	13.42	37.50	37.50
LYMPHO(XWBC)	17.0	32.0	32.0	34.0	55.0	22.0	32.0	5.0	5.0
LYMPHO(10 ¹³)	1.70	2.74	2.92	3.98	4.64	3.10	6.61	2.32	2.32
MONO(XWBC)	8.0	1.0	8.0	0.0	1.0	2.0	0.0	2.0	2.0
EOSINO(XWBC)	7.0	10.0	2.0	4.0	8.0	8.0	3.0	0.0	0.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	1.3	0.6	0.2	0.7	1.0	0.9	1.6	0.5	0.5
THR(10 ¹⁴ /CMH)	23	30	35	29	36	22	29	33	33
PROTEIN(SEC)	6.9	8.0	6.0	8.2	8.0	6.9	7.9	7.4	7.4

--BLOOD CHEM--

BUN(MGZ)	17.0	15.2	12.8	22.1	17.9	21.2	11.5	7.2	7.2
BS(MGZ)	80	73	76	70	56	76	62	94	94
AP(KAU)	6.7	3.7	3.6	13.2	7.4	7.6	18.9	128.3	128.3
SGOT(RFU/ML)	19	14	11	14	13	13	13	30	30
SGPT(RFU/ML)	21	13	14	13	12	10	5	7	7
BILI(MGZ)									
CL-(MEQ/L)	114	113	117	115	116	111	120	114	114
CA++(MGZ)	10.0	11.2	10.2	8.8	10.0	9.6	9.6	8.7	8.7
PCO2(MEQ/L)	24.2	27.2	24.0		24.0	27.8	29.0	21.0	21.0
PH	7.302	7.376	7.379		7.353	7.347	7.420	7.309	7.309
PROTEIN(GZ)	6.90	5.80	5.70		37.6	49.9	43.9	40.2	40.2
PCO2(MMHG)	47.7	45.7	39.6						

(All Values = gm%)

Sampling Time (Weeks)	Protein	Total	
		Albumin	Globulin
-3	6.4	2.7	3.7
0	5.8	2.2	3.6
13	6.2	4.0	2.2
20	6.8	2.2	4.6
39	3.5	2.0	1.5
50			

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Tissue HCB (PPM) Level at Necropsy

	<u>Bile</u>	<u>Fat</u>
	<u>Total</u>	<u>Lipid Extract</u>
	2,333	3,590

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1100F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>1/16/75</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>10:00 AM</u>
PATHOLOGY NUMBER	<u>76-26</u>	DATE KILLED	<u>1/16/75</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Poor</u>
AGE	<u>19 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>299</u>

SUMMARY:

DRUG INDUCED LESIONS

Arterioles, arteries, (peritracheal tissues, ovarian bursa, mediastinal lymph node, urinary bladder, omentum): +++ hyalinizing vasculitis-perivasculitis

Omentum: ++ focal fibrosis, +++ fat atrophy, (+) focal necrosis, + focal granulomatous inflammation

Omentum, large artery: + focal intimal mineralization

Liver: ++ subacute hepatitis, ++ bile duct hyperplasia, ++ chronic pericholangitis

Mediastinal lymph node: ++ focal necrosis

Thymus: ++ atrophy

OBSERVATIONS:

General Examination: The body is that of a emaciated small female beagle in poor condition. There is moderate dehydration; bony prominences are very pronounced. The hair coat is very dry and shows scruffy, focal alopecia and scaliness over the sternal area. The hair around the medial canthus of each eye is matted and covered with exudate.

Body Cavities and Serosal Surfaces: In the abdominal cavity, there is approximately 3 cc of

red semi opaque fluid. There is very little abdominal fat or subcutaneous fat. The omentum is condensed upon itself and tightly adherent to the descending colon.

Hemic and Lymphatic System: The thymus is very small and difficult to visualize.

Digestive System: The liver seems slightly large. On the capsular surface it has a nutmeg appearance. It also seems friable and the surface cracks easily on handling. In a focal area, around what appears to be a cholangiole, there is some thickening. The region affected is about 3 mm in diameter and light tan-gray. Only one such lesion is found throughout the liver which is otherwise very, very friable.

MICROSCOPIC OBSERVATIONS:

Liver: The liver shows a moderate subacute hepatitis characterized by bile duct hyperplasia and chronic pericholangitis. In the portal areas, there is moderate fibrosis surrounding bile ducts and moderate subacute inflammation with polymorphonuclear leukocytes and larger numbers of mononuclear cells. In addition, in portal areas there are macrophages which contain a light green pigment. A focal area of the parenchyma was a very large abscess with tremendous numbers of polymorphonuclear leukocytes in the center and areas of necrosis around the margin.

Trachea: The peritracheal fat shows a very pronounced subacute inflammatory process. There are numerous mononuclear and polymorphonuclear leukocytes dispersed through the tissue. In addition, there are a few plasma cells and some lymphoreticular cells and also evidence of fibrosis. Arterioles within this area show hyalinization of their walls and proliferation of the perithelial cells. Some of these vessels show a very pronounced perivascularitis.

Ovaries: In the periovarian tissues adjacent to the fallopian tube is a very pronounced subacute inflammatory process with numerous morphonuclear leukocytes, plasma cells, lymphocytes, and lymphoreticular cells. Small arterioles in the adjacent area have hyalinized walls in which inflammatory cells are noted. In addition, there are numerous inflammatory cells in the peri-adventitia and in some cases there appears to be a perithelial and endothelial proliferation.

Mediastinal lymph node: These nodes appear to be slightly less cellular than normal. In a cortical area, there is a large arteriole which shows hyalinization and moderate numbers of polymorphonuclear leukocytes and mononuclear cells throughout the wall. The endothelium in this vessel appears to have proliferated. Focal hemorrhage and necrosis is also present in the cortex of the node.

Thymus: ++ atrophy.

Ileum: + lymphoid atrophy.

Urinary bladder: A large arterioles just below the serosa of the bladder shows hyalinization of the wall and a very, very pronounced subacute vasculitis with numerous polymorphonuclear leukocytes, mononuclear cells and lymphoreticular cells in the surrounding tissues. Acute and chronic inflammatory cells are within the wall of the vessel and beneath the proliferating endothelium.

Omentum: Visible within the omentum are focal areas of granulomatous inflammation. In these areas there are numerous macrophages and a few polymorphonuclear leukocytes. In the same areas there appears to be focal fat necrosis. A few eosinophils are present. In focal areas of the omentum there is a marked focal subacute perivascularitis with moderate numbers of mononuclear cells, primarily lymphocytes surrounding small arterioles. Moderate focal fibrosis is also present. Large arteries show focal subintimal mineralization and there is severe atrophy of fat.

ANIMAL ID: D01098
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 10
 RX-DATE: 3/24/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/24 4/22 6/16 8/13 12/11 3/09
 DAY: 20- 0 29 84 142 262 351

--HEMATOLOGY--

HCT(%)	40	43	43	47	41	44	43
HGB(G%)	14.5	15.2	15.6	16.9	13.4	15.3	15.2
RBC(10 ¹⁶ /CMH)	5.47	5.61	5.94	7.11	5.74	6.07	6.47
WBC(10 ¹³ /CMH)	9.80	8.61	9.21	5.26	9.94	10.71	14.16
NEUT,I(%)	0.0	0.0	0.0	0.0	0.0	1.0	0.0
NEUT,M(%)	67.0	71.0	65.0	39.0	69.0	51.0	59.0
NEUT,M(10 ¹³)	6.57	6.11	5.99	2.05	6.86	5.46	8.35
LYMPHO(%)	21.0	21.0	27.0	55.0	18.0	43.0	40.0
LYMPHO(10 ¹³)	2.06	1.81	2.49	2.89	1.79	4.61	5.66
MONO(%)	9.0	1.0	3.0	0.0	4.0	4.0	0.0
EOSINO(%)	3.0	4.0	5.0	6.0	9.0	1.0	1.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORML(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	0.7	0.3	0.5	0.1	0.5	0.8	0.4
THR(10 ¹⁴ /CMH)	45	20	27	27	13	18	19
PROTIME(SEC)	6.4	8.4	6.9	7.9	6.4	7.9	7.4

--BLOOD CHEM--

BUN(MG%)	16.2	18.4	21.2	22.0	19.9	11.4	17.0
BS(MG%)	86	89	89	70	101	77	75
AP(KAU)	5.1	5.1	4.3	2.1	3.1	4.4	4.7
SGOT(RFU/ML)	13	10	14	14	8	9	14
SGPT(RFU/ML)	11	12	14	12	9	7	12
BILI(MG%)							
CL-(MEQ/L)	118	114	116	113	110	114	115
CA++(MG%)	10.4	10.2	10.2	10.4	9.8	9.6	9.8
PCO2(MEQ/L)	25.8	23.0	23.8	22.2	27.8	30.5	22.8
PH	7.351	7.337	7.373	7.342	7.313	7.439	7.355
PROTEIN(G%)	6.10	6.00	6.20	40.0	53.4	44.6	6.20
PCO2(MMHG)	45.4	41.9	39.2				39.5

Serum Electrophoresis

(All Values = gm%)

Necropsy Date: 14 April 1976
Day: 388

Dog No.: 1098
Dose Level (Mg/Day): 1000

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.6	2.9	3.7	0.783	0.4	0.7	0.9	1.1	0.5
0	6.0	2.2	3.8	0.584	1.1	0.8	0.4	0.8	0.7
13	15.1	10.9	4.2	2.636	0.8	1.3	1.7	0.0	0.4
20	6.9	2.3	4.6	0.488	0.9	1.1	1.4	-	1.2
39	6.4	3.2	3.2	1.000	0.8	0.7	0.5	0.6	0.7
50	6.7	3.9	2.8	1.432	1.0	0.4	0.3	0.9	0.1

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
637	700

Bile
45.7

ANIMAL NUMBER	.	.	.	.	(A/3-10)	D1098F
DAY ONE DATE	.	.	.	.	.	032475
INITIAL BODY WEIGHT	.	.	.	.	.	10.3 Kg
FINAL BODY WEIGHT	.	.	.	.	.	

COMPOUND	HCB
DOSE	1000 mg/dog/day
ROUTE	oral

Treatment Date	AIAU/11-16)	042275	061975	081375	5121275	030976
Day in Study	I(AU/17-19)	30	88	143	264	352
Sp. Gr.	R(U1/20-24)	1.060	1.050	1.045	1.062	1.058
pH	R(U1/25-29)	6	8	6	6	5.5
Sugar	I(U1/30-34)	0	0	0	0	0
Ketones	I(U1/35-39)	0	0	0	0	0
Blood	I(U1/40-44)	0	0	0	0	0
Protein	I(U1/45-49)	trace	1+	trace	1+	trace

		MICROSCOPIC	
Triple Phosphates	I(U2/20-24)		
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)		
Other	A(U2/35-39)	bact. *	
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0-1 gran.	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-4	0-3
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-3	0-3
Mucous	I(U2/60-69)	yellow	yellow
Appearance	I(U2/70-90)	yellow	yellow

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1098F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>4/14/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>2:00 PM</u>
PATHOLOGY NUMBER	<u>76-2569</u>	DATE KILLED	<u>4/14/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Fair</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>388</u>

SUMMARY:

DRUG INDUCED LESIONS

Omentum, small intestine, liver: + focal fibrous adhesions

Stomach, fundus, pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

General Examination: The body is that of a female beagle in fair condition with a dry, scurfy hair coat. There is marked epiphora affecting a 5 cm² area near the medial canthus of each eye.

Body Cavities and Serosal Surfaces: Small focal adhesions are present between the omentum and mesentery of the small intestine and between the omentum and cardiac lobe of the liver.

Digestive System: The gastric mucosa along the lesser curvature in the region of the pyloric antrum is covered by approximately 100 small nodules about 2 mm in diameter. About 10 similar nodules are present in the fundus.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa are a moderate number of small and medium sized lymphoid nodules.

Omentum: In the omentum are some very small focal areas of fibrosis and subchronic inflammation. In these areas there is increased collagen deposition and a few mononuclear cells mainly lymphocytes and plasma cells. The distribution of these areas is random and they are minimal in extent.

ANIMAL ID: D01104
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/24	4/22	6/16	8/13	12/11	3/09
DAY:	18-	0	29	84	142	259	348
---HEMATOLOGY---							
HCT(%)	44	46	44	48	49	47	42
HGB(GZ)	15.8	16.6	16.0	14.7	15.3	16.1	14.5
RBC(10 ¹⁶ /CMM)	6.02	6.19	6.02	6.15	6.23	6.61	5.98
WBC(10 ¹³ /CMM)	12.12	10.41	13.89	10.77	11.38	11.17	19.50
NEUT,I(%)	0.0	0.0	0.0	0.0	1.0	1.0	1.0
NEUT,M(%)	67.0	56.0	66.0	59.0	77.0	47.0	64.0
NEUT,M(10 ¹³)	8.12	5.83	9.17	6.35	8.76	5.25	12.48
LYMPHO(%)	27.0	41.0	23.0	35.0	14.0	45.0	28.0
LYMPHO(10 ¹³)	3.27	4.27	3.19	3.77	1.59	5.03	5.46
MONO(%)	2.0	0.0	4.0	0.0	5.0	4.0	3.0
EOSINO(%)	4.0	3.0	7.0	0.0	3.0	3.0	4.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	1.1	0.8	0.6	0.4	0.3	0.1	2.1
THR(10 ¹⁴ /CMM)	28	30	42	29	23	30	50
PROTIME(SEC)	6.4	9.9	6.4	7.8	7.0	8.4	7.9

---BLOOD CHEM---

BUN(MGZ)	22.0	19.2	17.0	11.5	20.4	8.2	11.5
BS(MGZ)	64	83	85	84	108	83	73
AP(KAU)	4.5	5.3	3.9	5.9	2.4	3.9	3.3
SGOT(RFU/ML)	13	15	13	11	9	10	19
SGPT(RFU/ML)	15	15	15	9	8	9	12
BILI(MGZ)	112	111	115	107	112	114	115
CL-(MEQ/L)	10.2	11.0	10.8	10.2	9.6	9.0	10.0
CA++(MGZ)	24.0	26.8	25.3	21.2	26.5	28.2	24.8
PCO2(MEQ/L)	7.324	7.377	7.385	7.406	7.311	7.434	7.383
PH	6.40	6.20	6.40	33.0	51.2	41.1	5.70
PROTEIN(GZ)	45.0	44.9	41.1	33.0	51.2	41.1	40.2
PCO2(MMHG)							

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1104 Necropsy Date: 13 April 1976
 Dose Level (Mg/Day): 1000 Day: 387

Sampling Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin							
-3	6.5	2.4	4.1		0.568	1.2	1.0	0.7	0.6	0.7
0	6.2	-	-		-	-	-	-	-	-
13	14.9	9.7	5.2		1.872	0.9	2.0	2.0	0.0	0.3
20	7.6	2.4	5.2		0.472	0.9	1.6	0.4	1.2	1.1
39	5.8	3.2	2.6		1.227	0.6	0.6	0.5	0.4	0.4
50	6.1	3.6	2.5		1.449	0.5	0.6	0.3	1.1	0.2

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Tissue HCB (PPM) Level at Necropsy

Fat	
Bile	
42.8	
Total	Lipid Extract
1,181	1,452

URINALYSIS

ANIMAL NUMBER.		(A3-10)	D1104F
DAY ONE DATE			032475
INITIAL BODY WEIGHT.			7.8 Kg
FINAL BODY WEIGHT			

COMPOUND		HCB
DOSE		. 1000 mg/dog/day
ROUTE		oral

Treatment Date		A(AU/11-16)	042275	061975	081375	121275	030376				
Day in Study		I(AU/17-19)	30	88	143	264	352				
Sp. Gr.		R(U1/20-24)	1.052	1.040	1.032	1.058	1.058				
pH		R(U1/25-29)	8	9	6	6	6				
Sugar		I(U1/30-34)	0	0	0	0	0				
Ketones		I(U1/35-39)	0	0	0	0	0				
Blood		I(U1/40-44)	0	0	0	0	1+				
Protein		I(U1/45-49)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Protein		I(U2/55-59)	trace	trace	trace	1+	1+				

REAGENT STRIP

Treatment Date		A(U2/20-24)	042275	061975	081375	121275	030376				
Day in Study		I(U2/25-29)	30	88	143	264	352				
Sp. Gr.		R(U2/30-34)	1.052	1.040	1.032	1.058	1.058				
pH		R(U2/35-39)	8	9	6	6	6				
Sugar		I(U2/40-44)	0	0	0	0	0				
Ketones		I(U2/45-49)	0	0	0	0	0				
Blood		I(U2/50-54)	0	0	0	0	1+				
Pro											

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1104F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>4/13/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>2:00 PM</u>
PATHOLOGY NUMBER	<u>76-2567</u>	DATE KILLED	<u>4/13/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Poor</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>387</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum, + lymphoid hyperplasia

OBSERVATIONS:

General Examination: The body is that of a thin female beagle in poor condition. The hair coat is dry and there is considerable shedding. There is a bilateral conjunctivitis.

Digestive System: In a 3 cm² area of the gastric mucosa along the lesser curvature near the junction of the body and pyloric antrum is an aggregation of lymphoid nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the body of the stomach were a moderate number of very small lymphoid nodules in the mucosa. Starting in the area of the pyloric antrum lymphoid nodules became prominent and confluent. These nodules were located in the mucosa. In addition there were a few very small lymphoid nodules.

ANIMAL ID: D01109
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/24/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 100.000000
 (MG/DOG): 1000.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/24	4/22	6/16	8/13	12/11	3/09
DAY:	18-	0	29	84	142	262	351
--HEMATOLOGY--							
HCT(%)	45	42	40	44	45	51	44
HGB(GZ)	16.1	15.3	14.4	15.5	16.3	15.3	16.8
RBC(10 ¹⁶ /CMM)	6.17	6.32	5.68	6.00	6.59	6.49	6.22
WBC(10 ¹³ /CMM)	17.93	12.89	16.54	17.81	18.74	22.30	22.32
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	6.0	1.0	0.0
NEUT,M(ZWBC)	62.0	65.0	66.0	59.0	64.0	75.0	67.0
NEUT,M(10 ¹³)	11.12	8.38	10.92	10.51	11.99	16.73	14.95
LYMPHO(ZWBC)	30.0	30.0	27.0	37.0	25.0	18.0	26.0
LYMPHO(10 ¹³)	5.38	3.87	4.47	6.59	4.69	4.01	5.80
MONO(ZWBC)	2.0	1.0	4.0	1.0	1.0	2.0	1.0
EOSINO(ZWBC)	6.0	4.0	3.0	3.0	4.0	4.0	6.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.4	0.7	0.4	0.3	0.4	0.7	1.0
THR(10 ¹⁴ /CMM)	32	35	36	37	16	21	41
PROTIME(SEC)	6.9	7.0	5.9	6.9	6.5	7.9	7.9

--BLOOD CHEM--

BUN(MGX)	22.6	19.7	21.2	16.6	22.8	16.6	12.8
BS(MGX)	90	93	84	73	100	83	73
AP(KAU)	4.6	4.8	3.7	5.3	3.6	3.7	5.6
SGOT(RFU/ML)	20	25	14	15	15	9	14
SGPT(RFU/ML)	15	17	16	12	11	5	9
BILI(MGX)							
CL-(MEQ/L)	117	114	115	111	111	113	118
CA+(MGZ)	10.6	10.6	10.2	10.0	9.6	10.0	9.8
PCO2(MEQ/L)	20.2	23.6	25.0	25.2	26.0	28.8	24.5
PH	7.245	7.300	7.375	7.323	7.300	7.429	7.382
PROTEIN(GZ)	6.40	6.00	5.80				6.60
PCO2(MMHG)	45.4	46.6	41.5	47.0	51.6	42.7	40.0

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1109

Necropsy Date: 13 April 1976

Dose Level (Mg/Day): 1000

Day: 387

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	a-1	a-2	β-1	β-2	γ
	Protein	Albumin	Globulin						
-3	6.9	2.4	4.5	0.545	1.2	1.0	0.9	0.7	0.7
0	6.0	1.9	4.1	0.456	1.0	1.0	0.5	0.9	0.7
13	15.0	8.3	6.7	1.242	2.9	0.0	3.6	0.0	0.2
20	7.4	2.7	4.7	0.577	0.7	1.4	0.9	0.7	0.9
39	6.5	3.2	3.3	0.974	0.6	0.9	0.6	0.5	0.6
50	6.7	4.2	2.5	1.649	0.5	0.5	1.0	0.0	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
Bile	Lipid Extract
39.8	436
Total	374

URINALYSISANIMAL NUMBER. (A/3-10) D1109MDAY ONE DATE 032475INITIAL BODY WEIGHT. 9.3 Kg

FINAL BODY WEIGHT

COMPOUND HCB
DOSE 1000 mg/dog/day

ROUTE oral

Treatment Date	AI(AU/11-16)	042275	061975	081375	121275	030976
Day in Study	II(AU/17-19)	30	88	143	264	352
Sp. Gr.	RI(U1/20-24)	1.044	1.040	1.045	1.064	1.044
pH	RI(U1/25-29)	8	9	6	6	6
Sugar	II(U1/30-34)	0	0	0	0	0
Ketones	II(U1/35-39)	0	0	0	0	0
Blood	II(U1/40-44)	0	0	0	0	trace
Protein	II(U1/45-49)	trace	1+	1+	1+	trace
REAGENT STRIP						
MICROSCOPIC						
Triple Phosphates	II(U2/20-24)		2+		1+	0
Uric Acid	II(U2/25-29)					
Calcium Salts	II(U2/30-34)					
Other	AI(U2/35-39)	bact. *	yeast		sperm	sperm
Casts/LPF 100X (Avg/Field)	II(U2/40-44)	0-1	0	waxy	0	0
RBC/HPF 400X (Avg/Field)	II(U2/45-49)	0-2	0	0	0	8-10
WBC/HPF 400X (Avg/Field)	II(U2/50-54)	0	0-1	*	30-50	20-30
EPITH/HPF 400X (Avg/Field)	II(U2/55-59)	0-3	0	0-1	many	8-10
Mucous	II(U2/60-69)					
Appearance	II(U2/70-80)	yellow	yellow	cl. y	cl. y	cl. dk y

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1109M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032475</u>	NECROPSY DATE	<u>4/13/75</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>1,000</u>	HOUR DIED	<u>11:00 AM</u>
PATHOLOGY NUMBER	<u>76-2566</u>	DATE KILLED	<u>4/13/75</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>387</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

General Examination: The body is that of a male beagle in good condition. Epiphora is present.

Digestive System: The gastric mucosa is 2.5 x 5 cm area of the pyloric antrum is covered with small nodular bodies approximately 2.5 mm in diameter.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous prominent and confluent lymphoid nodules. These nodules are otherwise unremarkable. Some have active germinal centers with a peripheral mantle of lymphocytes.

ANIMAL ID: D01076
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 10.00000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/25 4/23 6/17 8/14
 DAY: 7- 0 29 84 142

--HEMATOLOGY--

HCT(%)	43	44	47	46	44
HGB(GZ)	15.5	15.5	17.3	15.8	15.0
RBC(10 ¹⁶ /CMH)	6.42	5.72	6.25	5.81	6.07
WBC(10 ¹³ /CMH)	9.32	10.49	10.57	11.56	12.20
NEUT,I(2WBC)	0.0	0.0	2.0	0.0	1.0
NEUT,M(2WBC)	37.0	49.0	49.0	41.0	45.0
NEUT,N(10 ¹³)	3.45	5.14	5.18	4.74	5.49
LYMPHO(2WBC)	53.0	42.0	36.0	51.0	45.0
LYMPHO(10 ¹³)	4.94	4.41	3.81	5.90	5.49
MONO(2WBC)	0.0	4.0	5.0	3.0	4.0
EOSINO(2WBC)	10.0	5.0	8.0	5.0	5.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.6	0.9	1.1	0.2	0.5
THR(10 ¹⁴ /CMH)	23	18	18	11	14
PROTIME(SEC)	7.9	9.4	7.9	8.5	7.9

--BLOOD CHEM--

BUN(MGZ)	13.3	19.2	21.9	16.7	22.0
BS(MGZ)	96	81	86	79	80
AP(KAU)	2.1	1.9	1.5	2.6	2.4
SGOT(RFU/ML)	14	13	11	13	8
SGPT(RFU/ML)	14	15	12	10	7
BILI(MGZ)					
CL-(MEQ/L)	115	116	110	108	115
CA++(MGZ)	9.6	10.0	10.2	10.8	10.0
PCO2(MEQ/L)	24.2	22.5	26.2	22.2	27.0
PH	7.355	7.328	7.376	7.281	7.337
PROTEIN(GZ)	5.90	6.10	5.60		
PCO2(MMHG)	42.3	41.5	44.1	45.9	49.3

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1076 Necropsy Date: 14 August 1975
 Dose Level (Mg/Day): 100 Day: 143

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.1	3.1	3.0	1.036	0.8	0.7	0.4	0.8	0.3
13	-	-	-	-	-	-	-	-	-
20	6.4	2.6	3.8	0.680	0.7	1.0	0.5	0.8	0.9
39				Sacrificed					
50									

Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	6.7	
	140	162

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1076F</u>	NECROPSY DATE	<u>8/14/75</u>
DAY ONE DATE	<u>2/25/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>2:00 PM</u>
DOSE Mg/Da	<u>100</u>	DATE DIED	<u>8/14/75</u>
PATHOLOGY NUMBER	<u>75-5951</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>12 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			

SUMMARY:

DRUG INDUCED LESIONS

Stomach: fundus, pyloric antrum, ++ lymphoid hyperplasia

Epiglottis: ++ focal lymphoid hyperplasia

Esophagus: (+) focal lymphoid hyperplasia

OBSERVATIONS:

Respiratory System: Along the margin of the epiglottis are slightly raised thickened areas which appear to be coalescing nodules varying from 2-4 mm in diameter. The lungs are pink and spongy with the exception of some focal lesions visible on various lobes. Microscopically, there is focal lymphoid hyperplasia in the submucosa of the epiglottis.

Digestive System: In the fundic mucosa there are numerous, fine, slightly raised nodules which coalesce and vary from 3-4 mm. Similar nodules are visible in the pyloric antrum. At the glottis-esophageal junction some fine, barely visible focal nodules can be seen in the mucosa which may represent normal lymphoid nodules. Microscopically, the fundic mucosa and esophagus show lymphoid hyperplasia with numerous active lymphoid nodules.

ANIMAL ID: D01114
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 5/15/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.00000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 1/17 3/25 4/23 5/15
 DAY: 8- 0 29 51

--HEMATOLOGY--

HCT(%)	48	43	43
HGB(GZ)	18.0	15.4	15.8
RBC(10 ¹⁶ /CMH)	6.98	5.90	6.01
WBC(10 ¹³ /CMH)	11.66	11.92	17.50
NEUT,I(2WBC)	0.0	0.0	4.0
NEUT,M(2WBC)	58.0	55.0	76.0
NEUT,M(10 ¹³)	6.76	6.56	13.30
LYMPHO(2WBC)	37.0	41.0	18.0
LYMPHO(10 ¹³)	4.31	4.89	3.15
MONO(2WBC)	3.0	0.0	1.0
EOSINO(2WBC)	2.0	4.0	1.0
BASO(2WBC)	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0
RET(2RBC)	0.6	0.2	1.2
THR(10 ¹⁴ /CMH)	31	40	15
PROTIME(SEC)	6.9	7.4	6.0

--BLOOD CHEM--

BUN(MGZ)	16.9	13.0	13.8	29.6
BS(MGZ)	89	76	73	11
AP(KAU)	4.3	10.4	3.7	42.2
SGOT(RFU/ML)	22	17	14	47
SGPT(RFU/ML)	22	16	14	14
BILI(MGZ)				
CL-(MEQ/L)	115	113	112	103
CA++(MGZ)	11.3	10.4	9.6	9.0
PCO2(MEQ/L)		26.0	26.2	21.8
PH		7.343	7.378	7.161
PROTEIN(GZ)	5.90	6.50	5.70	
PCO2(MMHG)		46.9	43.8	58.9

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1114 Necropsy Date: 15 May 1976
 Dose Level (Mg/Day): 100 Day: 52

Sampling Time (Weeks)	Total					Albumin/Globulin (Ratio)				
	Protein	Albumin	Globulin	α -1	α -2		β -1	β -2	γ	
-3	-	-	-	-	-	-	-	-	-	-
0	6.5	3.0	3.5	1.1	0.9	0.833	0.6	0.6	0.3	-
13										115
20										
39										
50										

Died

Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	-	-
216	-	-

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1114F</u>	NECROPSY DATE	<u>5/15/75</u>
DAY ONE DATE	<u>3/25/75</u>	EUTHANIZED WITH	<u>—</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>8:45 AM</u>
DOSE Mg/Da	<u>100</u>	DATE DIED	<u>5/15/75</u>
PATHOLOGY NUMBER	<u>75-3866</u>	PRENECROPSY CONDITION	<u>Poor</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Good</u>
AGE	<u>10 mo</u>	POSTMORTEM INTERVAL	<u>45 minutes</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>1/2 hr.</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u> </u>

SUMMARY:

DRUG INDUCED LESIONS

Lungs: +++ focal acute hemorrhagic bronchopneumonia

Tracheo-bronchial lymph node: ++ atrophy

Thymus: +++ atrophy

Ileum: Peyer's patches, ++ atrophy

Spleen: lymphoid nodules, ++ atrophy

Colon: lymphoid nodules, ++ atrophy, (+) focal submucosal abscess

Mediastinal lymph node: + atrophy

Parotid lymph node: + atrophy

Heart: epicardial fat, ++ serous atrophy

MICROSCOPIC OBSERVATIONS:

Lungs: focal acute hemorrhagic bronchopneumonia. Several lobes of the lung show an extensive pulmonary edema and the presence of many polymorphonuclear leukocytes in the alveolar spaces and bronchioles. In addition, there is considerable hemorrhage within alveolar spaces. The

lesions are focal and do not involve all lobes of the lung.

Heart: The epicardial fat in the coronary groove appears to have undergone serous atrophy. The lipocytes appear to be less distended than normal and have a fragmented appearance.

Tracheal and bronchial lymph nodes: The bronchial lymph nodes appear to be slightly atrophic and less cellular than normal.

Mesenteric lymph node: lymphoid atrophy.

Thymus: lymphoid atrophy.

Spleen: lymphoid atrophy.

ANIMAL ID: D01127
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/25 4/23 6/17 8/14
 DAY: 7- 0 29 84 142

--HEMATOLOGY--

HCT(%)	41	44	42	47	48
HGB(GZ)	15.0	16.0	15.0	16.3	17.1
RBC(10 ¹⁶ /CMH)	6.15	6.45	6.22	6.34	7.15
WBC(10 ¹³ /CMH)	8.23	8.93	11.88	9.89	10.55
NEUT,I(XWBC)	0.0	0.0	2.0	1.0	2.0
NEUT,M(XWBC)	53.0	56.0	56.0	64.0	53.0
NEUT,M(10 ¹³)	4.36	5.00	6.65	6.33	5.59
LYMPHO(XWBC)	36.0	39.0	34.0	28.0	36.0
LYMPHO(10 ¹³)	2.96	3.48	4.04	2.77	3.80
MONO(XWBC)	0.0	2.0	4.0	3.0	2.0
EOSINO(XWBC)	11.0	4.0	4.0	4.0	7.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	0.3	0.3	0.1	0.2	0.1
THR(10 ¹⁴ /CMH)	35	43	24	20	23
PROTIME(SEC)	8.5	7.4	6.6	6.9	6.9

--BLOOD CHEM--

BUN(MGZ)	13.0	14.0	16.8	16.0	14.2
BS(MGZ)	85	90	96	82	90
AP(KAU)	4.4	10.8	2.9	2.4	3.3
SGOT(RFU/ML)	14	12	11	13	7
SGPT(RFU/ML)	16	15	12	12	10
BILI(MGZ)					
CL-(MEQ/L)	115	114	112	112	112
CA++(MGZ)	10.6	10.8	10.4	10.2	10.6
PCO2(MEQ/L)	25.2	26.8	24.2	25.2	25.2
PH	7.349	7.334	7.345	7.331	7.355
PROTEIN(GZ)	6.70	6.40	6.00		
PCO2(MMHG)	44.7	49.3	43.2	46.6	43.9

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1127
Dose Level (Mg/Day): 100

Necropsy Date: 14 August 1975
Day: 143

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.4	3.3	3.1	1.075	0.8	0.6	0.7	0.5	0.5
13	-	-	-	-	-	-	-	-	-
20	7.6	2.6	5.0	0.526	0.9	1.3	1.1	0.7	0.9
39				Sacrificed					
50									

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
3.9	69	94

URINALYSIS

ANIMAL NUMBER.		(A/3-10)	D1127M
DAY ONE DATE			032575
INITIAL BODY WEIGHT.			10.1 Kg
FINAL BODY WEIGHT			

COMPOUND	HCBr
DOSE	100 mg/dog/day
ROUTE	oral

Treatment Date		A(AU/11-16)	042375	061975	081475				
Day in Study		I(AU/17-19)	29	86	142				
Sp. Gr.		R(IU/20-24)	1.010	1.023	1.034				
pH		R(IU/25-29)	6	8	6				
Sugar		I(U1/30-34)	0	0	0				
Ketones		I(U1/35-39)	0	0	0				
Blood		I(U1/40-44)	0	0	0				
Protein		I(U1/45-49)	1+	trace	trace				
REAGENT STRIP									
MICROSCOPIC									
Triple Phosphates		I(U2/20-24)		1+	2+				
Uric Acid		I(U2/25-29)							
Calcium Salts		I(U2/30-34)	heavy						
Other		A(U2/35-39)	0	yeast*					
Casts/LPF 100X (Avg/Field)		I(U2/40-44)							
RBC/HPF 400X (Avg/Field)		I(U2/45-49)							
WBC/HPF 400X (Avg/Field)		I(U2/50-54)	*	0	0				
EPITH/HPF 400X (Avg/Field)		I(U2/55-59)	3-10	5-10	0-1				
Mucous		I(U2/60-69)							
Appearance		I(U2/70-80)	yellow/t. y	yellow	yellow				

* Too numerous to count

**** Moderate**

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1127M</u>	NECROPSY DATE	<u>8/14/75</u>
DAY ONE DATE	<u>3/25/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>9:45 AM</u>
DOSE Mg/Da	<u>100</u>	DATE DIED	<u>8/14/75</u>
PATHOLOGY NUMBER	<u>75-5947</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>10 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u> </u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach: fundus, pylorus, +++ lymphoid hyperplasia

Duodenum: duodenal papilla, + focal hemorrhage

Ileum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: At the junction of the body and fundus of the stomach, there are numerous small nodules approximately 2-4 mm in diameter in the mucosa; a few of these nodules are also present in fundic area of the stomach. In the mucosa of the duodenum, starting immediately at the pylorus, there are two little nodules which have focal, red spots on them approximately 1 mm in diameter. The nodules themselves are about a cm in diameter. The mucosa of the small and large intestine is unremarkable. The duodenal papilla where the common bile duct and the other bile duct open, is distinctly red and raised into the lumen of the duodenum. The small intestine shows no fibrous adhesions. It lays out flat on opening.

MICROSCOPIC OBSERVATIONS:

Stomach: Lymphoid hyperplasia, in the mucosa there are small and large lymphoid nodules. In the region of the pylorus there are numerous very large and coalescent lymphoid nodules.

Duodenum: In the region of the duodenal papilla there is focal hemorrhage in the mucosa. The remaining portion of the duodenum is unremarkable except for sloughing of the superficial epithelium covering villi.

Ileum: The mucosa of the ileum is unremarkable. In the submucosa there are numerous lymphoid nodules, some of which appear to considerably larger than normal.

ANIMAL ID: D01121
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/18	3/25	4/23	6/17	8/14
DAY:	7-	0	29	84	142
--HEMATOLOGY--					
HCT(Z)	49	47	48	50	49
HGB(GZ)	17.5	16.7	18.0	18.2	17.0
RBC(10 ⁶ /CMH)	7.14	6.48	6.96	6.92	6.74
WBC(10 ³ /CMH)	10.38	10.57	9.86	13.11	11.76
NEUT,I(ZWBC)	0.0	0.0	3.0	0.0	0.0
NEUT,M(ZWBC)	41.0	57.0	38.0	52.0	70.0
NEUT,H(10 ³)	4.26	6.02	3.75	6.82	8.23
LYMPHO(ZWBC)	51.0	37.0	53.0	34.0	25.0
LYMPHO(10 ³)	5.29	3.91	5.23	4.46	2.94
MONO(ZWBC)	4.0	3.0	4.0	6.0	2.0
EOSINO(ZWBC)	4.0	3.0	2.0	8.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.6	0.4	0.4	1.6	1.0
THR(10 ⁴ /CMH)	27	40	22	16	20
PROTIME(SEC)	9.5	8.4	6.5	6.9	6.9

--BLOOD CHEM--

BUN(MGZ)	17.5	15.0	18.1	18.2	13.6
BS(MGZ)	79	83	82	74	87
AP(KAU)	2.4	3.3	1.8	2.6	2.6
SGOT(RFU/ML)	14	17	12	15	8
SGPT(RFU/ML)	15	22	17	15	13
BILI(MGZ)					
CL-(MEQ/L)	116	115	113	108	115
CA++(MGZ)	10.0	10.6	10.0	10.4	10.4
PCO2(MEQ/L)	22.2	25.8	27.0	25.0	24.8
PH	7.367	7.358	7.379	7.336	7.404
PROTEIN(GZ)	6.30	6.00	5.40	45.7	38.6
PCO2(MMHG)	37.8	44.2	44.5		

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1121 Necropsy Date: 14 August 1975
 Dose Level (Mg/Day): 100 Day: 143

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)					
	Protein	Albumin	Globulin		α -1	α -2	β -1	β -2	γ
-3	-	-	-	-	-	-	-	-	-
0	6.0	2.9	3.1	0.965	0.8	0.8	0.6	0.5	0.4
13	-	-	-	-	-	-	-	-	-
20	6.9	2.4	4.5	0.531	0.9	1.2	0.9	0.6	0.9
39				Sacrificed					
50									

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Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	11.6	
	281	367

URINALYSIS

ANIMAL NUMBER (A/3-10) D1121M
 DAY ONE DATE 032575
 INITIAL BODY WEIGHT 9.7 Kg
 FINAL BODY WEIGHT _____

COMPOUND HCB
 DOSE 100 mg/dog/day
 ROUTE oral

Treatment Date	A1(AU/11-16)	D42375061975	081475
Day in Study	I(AU/17-19)	29	86 142
Sp. Gr.	R(U1/20-24)	1.040	1.045 1.034
pH	R(U1/25-29)	8	9 6
Sugar	I(U1/30-34)	0	0 0
Ketones	I(U1/35-39)	0	0 0
Blood	I(U1/40-44)	0	0 0
Protein	I(U1/45-49)	0	1+ trace
REAGENT STRIP			
MICROSCOPIC			
Triple Phosphates	I(U2/20-24)		2+
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)	very	3+
Other	A(U2/35-39)		
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	waxy waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	0 0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	2-5	0 *
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-2	0-2 5-10
Mucous	I(U2/60-69)		
Appearance	I(U2/70-80)	c.y	yellow

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1121M</u>	NECROPSY DATE	<u>8/14/75</u>
DAY ONE DATE	<u>3/25/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>11:15 AM</u>
DOSE Mg/Da	<u>100</u>	DATE DIED	<u>8/14/75</u>
PATHOLOGY NUMBER	<u>75-5948</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>143</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach: fundus, pyloric antrum, ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the fundic and pyloric mucosa are numerous slightly raised gray nodules approximately 3-4 mm in diameter. These are very numerous and also coalesced in certain areas; they do not appear to be ulcerated nor is the mucosa irregular. Visible in the mucosa of the esophagus approximately 4 cm from the esophageal cardiac junction are 3 similar slightly raised gray nodules varying from 3-4 mm in diameter. In addition, in the mucosa of the proximal esophagus where it joins the glottis, there are several similar gray nodules varying from 3-5 mm in diameter; approximately 7 of these nodules are coalescent.

MICROSCOPIC OBSERVATIONS:

Stomach: In the fundic and pyloric mucosa there are numerous well developed lymphoid nodules.

In the mucosa of the body a few small lymphoid nodules are present. These were not prominent nor were they visible in the gross.

ANIMAL ID: D01079
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 22- 0 29 84 142 262 350

---HEMATOLOGY---

HCT(%)	42	37	43	45	43	46	55
HGB(GZ)	14.7	13.7	14.4	15.1	15.5	15.6	18.4
RBC(10 ¹⁶ /CMH)	5.34	5.64	6.12	5.84	6.67	6.81	7.75
WBC(10 ¹³ /CMH)	12.80	9.22	14.66	9.32	8.93	10.63	11.42
NEUT,I(ZWBC)	0.0	0.0	10.0	0.0	1.0	0.0	1.0
NEUT,M(ZWBC)	61.0	49.0	48.0	47.0	48.0	49.0	61.0
NEUT,M(10 ¹³)	7.81	4.52	7.04	4.38	4.29	5.21	6.97
LYMPHO(ZWBC)	35.0	39.0	35.0	42.0	39.0	26.0	26.0
LYMPHO(10 ¹³)	4.48	3.60	5.13	3.91	3.48	2.76	2.97
MONO(ZWBC)	3.0	1.0	3.0	5.0	5.0	15.0	8.0
EOSINO(ZWBC)	1.0	11.0	4.0	6.0	7.0	10.0	4.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.3	0.1	0.3	2.0	0.6	0.3	1.5
THR(10 ¹⁴ /CMH)	33	33	27	20	18	19	31
PROTIME(SEC)	7.9	8.5	7.4	8.4	7.5	7.4	7.4

---BLOOD CHEM---

BUN(MGZ)	16.8	10.5	13.4	18.1	12.2	20.9	16.5
BS(MGZ)	96	87	81	79	83	78	70
AP(KAU)	3.0	2.7	3.0	2.1	2.2	2.2	1.3
SGOT(RFU/ML)	17	17	15	13	9	10	17
SGPT(RFU/ML)	13	12	15	9	10	9	10
BILI(MGZ)							
CL-(MEQ/L)	117	113	112	111	113	112	121
CA+(MGZ)	10.2	10.2	9.6	10.6	10.4	10.4	10.8
PCO2(MEQ/L)	21.2	25.2	25.8	21.0	25.0	30.8	22.8
PH	7.242	7.332	7.355	7.321	7.364	7.478	7.277
PROTEIN(GZ)	6.60	6.60	5.60	39.3	42.8	41.0	7.40
PCO2(MMHG)	48.0	46.3	44.8				47.2

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1079

Dose Level (Mg/Day): 100

Necropsy Date: 8 April 1976

Day: 381

Sampling Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
		Albumin	Globulin						
-3	8.5	3.1	5.4	0.563	1.4	0.9	1.3	1.2	0.7
0	6.6	2.5	4.1	0.627	0.8	0.6	1.3	0.8	0.6
13	6.1	3.9	2.2	1.750	0.9	0.0	1.2	0.0	0.2
20	7.6	2.8	4.8	0.579	1.0	1.3	0.4	1.1	1.0
39	7.0	3.6	3.4	1.032	0.8	0.8	0.5	0.7	0.6
50	7.8	4.8	3.0	1.585	0.6	0.5	1.0	0.6	0.2

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
82	164

Bile
7.1

URINALYSIS

COMPOUND	• • • • •	HCB
DOSE	• • • • •	100 mg/dog/day
ROUTE	• • • • •	oral

ANIMAL NUMBER	(A/3-10)	D1079M
DAY ONE DATE		032575
INITIAL BODY WEIGHT		9.7 Kg
FINAL BODY WEIGHT		

Treatment Date	AIAU/11-16)	042375	061975	081475	121275	030978
Day in Study	I(U1/17-19)	29	86	142	263	351
Sp. Gr.	RI(U1/20-24)	1.027	1.050	1.040	1.040	1.036
pH	RI(U1/25-29)	7	9	7	6	6
Sugar	I(U1/30-34)	0	0	0	0	0
Ketones	I(U1/35-39)	0	0	0	0	0
Blood	I(U1/40-44)	0	0	0	0	0
Protein	I(U1/45-49)	trace	1+	trace	trace	0

REAGENT STRIP	
Triple Phosphates	I(U2/20-24)
Uric Acid	I(U2/25-29)
Calcium Salts	I(U2/30-34)
Other	A(U2/35-39)
Casts/LPF 100X (Avg/Field)	I(U2/40-44)
RBC/HPF 400X (Avg/Field)	I(U2/45-49)
WBC/HPF 400X (Avg/Field)	I(U2/50-54)
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)
Mucous	I(U2/60-69)
Appearance	I(U2/70-80)

MICROSCOPIC	
Triple Phosphates	I(U2/20-24)
Uric Acid	I(U2/25-29)
Calcium Salts	I(U2/30-34)
Other	A(U2/35-39)
Casts/LPF 100X (Avg/Field)	I(U2/40-44)
RBC/HPF 400X (Avg/Field)	I(U2/45-49)
WBC/HPF 400X (Avg/Field)	I(U2/50-54)
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)
Mucous	I(U2/60-69)
Appearance	I(U2/70-80)

mod.	1+	4+				

*** Too numerous to count**

**** Moderate**

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1079M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/8/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>2:30 PM</u>
PATHOLOGY NUMBER	<u>76-2463</u>	DATE KILLED	<u>4/8/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>381</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, fundus, body-pyloric antrum: ++ lymphoid hyperplasia

Prostate: +++ atrophy

Testes: +++ fibrosis and degeneration

OBSERVATIONS:

Urogenital System: The testes and prostate are small.

Digestive System: The mucosa of the stomach in the regions of the pyloric antrum and fundus is covered with approximately 150, 2-3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa of the stomach are numerous large and small, sometimes confluent lymphoid nodules.

Prostate: The prostate shows extensive atrophy. It is much smaller than normal and the acinar structures are poorly developed. No secretory product is visible. It is not clear if this is a drug related lesion.

Testes: The well developed epididymal tubules contain no spermatozoa or spermatogonia. The testicles show extensive fibrosis and a small complement of tubules are lined by Sertoli cells only. No evidence of spermatogenesis is present. Some pigment laden macrophages are visible in the fibrous tissue of the testicle. The pigment is granular and light gray-green. It is not clear if the testicular lesions are drug related.

ANIMAL ID: D01123
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 7- 0 29 84 142 262 350

--HEMATOLOGY--

HCT(%)	44	41	40	41	48	51	53
HGB(GZ)	15.8	15.1	14.6	15.5	16.5	17.2	18.0
RBC(10 ¹⁶ /CMH)	6.36	6.01	5.90	5.63	6.60	7.16	7.28
WBC(10 ¹³ /CMH)	16.94	14.07	13.66	15.21	14.95	18.56	19.62
NEUT,I(%WBC)	0.0	0.0	6.0	1.0	0.0	1.0	3.0
NEUT,M(%WBC)	25.0	55.0	48.0	56.0	58.0	64.0	57.0
NEUT,M(10 ¹³)	4.24	7.74	6.56	8.52	8.67	11.88	11.18
LYMPHO(%WBC)	61.0	39.0	36.0	29.0	34.0	26.0	33.0
LYMPHO(10 ¹³)	10.33	5.49	4.92	4.41	5.08	4.83	6.47
MONO(%WBC)	1.0	0.0	1.0	3.0	0.0	2.0	1.0
EOSINO(%WBC)	13.0	6.0	8.0	11.0	8.0	7.0	6.0
BASO(%WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%RBC)	1.1	0.8	0.2	0.9	0.9	1.1	0.9
THR(10 ¹⁴ /CMH)	11	38	15	25	14	23	16
PROTIME(SEC)	8.9	6.9	6.4	6.9	7.4	6.9	8.4

--BLOOD CHEM--

BUN(MGZ)	21.3	15.0	14.8	18.9	21.3	17.7	18.3
BS(MGZ)	77	80	86	74	84	80	69
AP(KAU)	3.6	3.6	2.2	3.6	3.1	2.1	2.9
SGOT(RFU/ML)	25	19	13	19	14	7	13
SGPT(RFU/ML)	16	13	14	11	12	6	9
BILI(MGZ)							
CL-(MEQ/L)	114	115	110	108	109	113	117
CA++(MGZ)		10.6	10.4	10.6	11.4	10.4	10.6
PCO2(MEQ/L)	25.8	26.0	26.2	26.0	24.0	28.8	23.8
PH	7.223	7.325	7.369	7.335	7.408	7.439	7.342
PROTEIN(GZ)	7.10	6.40	6.00				7.30
PCO2(MMHG)	60.6	48.5	44.5	47.9	37.1	41.5	42.7

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1123

Dose Level (Mg/Day): 100

Necropsy Date: 9 April 1976

Day: 382

Sampling Time (Weeks)	Total					γ
	Protein	Albumin	Globulin	Albumin/Globulin (Ratio)		
-3	-	-	-	-	-	-
0	6.4	2.4	4.0	0.601	0.8	0.4
13	-	-	-	-	-	-
20	8.3	3.1	5.2	0.592	0.9	1.2
39	7.1	3.7	3.4	1.104	0.6	0.6
50	7.8	3.8	4.8	0.950	0.7	0.3

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
335	408

Bile
17.8

Page

URINALYSIS

ANIMAL NUMBER (A/3-10) D1123M
 DAY ONE DATE 032575
 INITIAL BODY WEIGHT 8.9 Kg
 FINAL BODY WEIGHT
 COMPOUND HCB
 DOSE 100 mg/dog/day
 ROUTE oral

Treatment Date	AI(AU/11-16)	042375	062075	081475	121275	030976						
Day in Study	AI(AU/17-19)	29	87	142	263	351						
Sp. Gr.	RI(U1/20-24)	1.040	1.040	1.045	1.054	1.060						
pH	RI(U1/25-29)	6	8	6	7	7.5						
Sugar	II(U1/30-34)	0	0	0	0	0						
Ketones	II(U1/35-39)	0	0	0	0	0						
Blood	II(U1/40-44)	0	0	0	0	0						
Protein	II(U1/45-49)	0	1	1+	1+	1+						
REAGENT STRIP												
MICROSCOPIC												
Triple Phosphates	II(U2/20-24)		3+			1+						
Uric Acid	II(U2/25-29)											
Calcium Salts	II(U2/30-34)		mod.									
Other	AI(U2/35-39)		sperm*		sperm	sperm						
Casts/LPF 100X (Avg/Field)	II(U2/40-44)	0	waxy	waxy	0	0						
RBC/HPF 400X (Avg/Field)	II(U2/45-49)	0-2	0	0	1-3	0						
WBC/HPF 400X (Avg/Field)	II(U2/50-54)	0-3	2-4	0-1	40-50	2-3						
EPITH/HPF 400X (Avg/Field)	II(U2/55-59)	0-2	5-12	0-1	1-2	1-2						
Mucous	II(U2/60-69)		yellow	dk. y	cl dk y	cl dk y						
Appearance	II(U2/70-80)											

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1123M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/9/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>9:45 AM</u>
PATHOLOGY NUMBER	<u>76-2507</u>	DATE KILLED	<u>4/9/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>382</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, fundus, pyloric antrum and canal: +++ lymphoid hyperplasia

OBSERVATIONS:

General Examination: The body is that of a male beagle in good condition with a slight lacrimal discharge on the face.

Digestive System: The mucosa of the stomach in the areas of the fundus, pyloric antrum and extending into the pyloric canal is covered with many small, 2-3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa of the cardia and pyloric antrum are numerous small and large lymphoid nodules.

ANIMAL ID: D01082
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/05 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 20- 0 29 84 142 262 350

--HEMATOLOGY--

HCT(Z)	43	45	44	45	46	48	44
HGB(GZ)	15.8	16.5	16.4	15.2	15.7	16.7	15.2
RBC(10 ¹⁶ /CMH)	6.06	6.30	5.99	6.02	6.41	7.03	6.39
WBC(10 ¹³ /CMH)	11.31	10.80	7.38	11.74	14.80	19.87	21.74
NEUT,I(ZWBC)	0.0	0.0	12.0	1.0	0.0	4.0	1.0
NEUT,M(ZWBC)	69.0	47.0	41.0	59.0	33.0	59.0	69.0
NEUT,M(10 ¹³)	7.80	5.08	3.03	6.93	4.88	11.72	15.00
LYMPHO(ZWBC)	20.0	47.0	36.0	32.0	45.0	28.0	25.0
LYMPHO(10 ¹³)	2.26	5.08	2.66	3.76	6.66	5.56	5.44
MONO(ZWBC)	6.0	0.0	6.0	2.0	6.0	4.0	2.0
EOSINO(ZWBC)	5.0	6.0	5.0	6.0	16.0	5.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.4	0.1	0.1	0.7	0.8	0.7	0.9
THR(10 ¹⁴ /CMH)	27	15	16	12	18	22	34
PROTINE(SEC)	7.9	8.9	7.9	7.9	9.0	8.4	8.9

--BLOOD CHEM--

BUN(MGZ)	15.7	11.4	16.2	11.8	15.8	11.8	8.3
BS(MGZ)	78	68	75	64	78	67	51
AP(KAU)	3.3	2.2	1.5	1.5	2.7	2.5	2.5
SGOT(RFU/ML)	14	15	13	17	9	15	15
SGPT(RFU/ML)	19	14	19	15	12	10	20
BILI(MGZ)							
CL-(MEQ/L)	114	113	115	113	114	116	116
CA++(MGZ)	9.8		10.0	10.4	10.4	9.6	9.1
PCO2(MEQ/L)	24.0	26.5	26.0	22.4	25.2	33.0	24.6
PH	7.349	7.292	7.357	7.298	7.328	7.442	7.330
PROTEIN(GZ)	6.20	6.10	5.50	44.1	46.8	47.3	5.60
PCO2(MMHG)	42.6	53.5	45.5				45.5

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1082 Necropsy Date: 8 April 1976
 Dose Level (Mg/Day): 100 Day: 381

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	8.6	3.2	5.4	0.596	1.5	1.2	0.9	1.0	0.7
0	6.1	-	-	-	-	-	-	-	- 139 -
13	6.5	5.0	1.5	3.333	0.2	0.1	0.9	0.0	0.2
20	7.4	2.6	4.8	0.531	0.9	1.2	0.5	1.1	1.2
39	6.8	3.6	3.2	1.131	0.6	0.6	0.6	0.8	0.6
50	5.7	2.5	3.2	0.794	0.3	0.7	0.7	0.8	0.7

Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Total</u>
107.9	1723
	<u>Lipid Extract</u>
	3117

Page

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1082E
DAY ONE DATE 032575
INITIAL BODY WEIGHT. 9.4 Kg
FINAL BODY WEIGHT
COMPOUND HCB
DOSE 100 mg/dog/day
ROUTE oral

Treatment Date	AI(AU/11-16)	042475	061975	081475	121276	030976						
Day in Study	II(AU/17-19)	30	86	142	263	351						
Sp. Gr.	RI(U1/20-24)	1.060	1.045	1.050	1.062	1.060						
pH	RI(U1/25-29)	6	7	6	6	5.5						
Sugar	II(U1/30-34)	0	0	0	0	0						
Ketones	II(U1/35-39)	0	0	0	0	0						
Blood	II(U1/40-44)	0	0	0	0	0						
Protein	II(U1/45-49)	trace	1+	trace	1+	trace						
REAGENT STRIP												
MICROSCOPIC												
Triple Phosphates	II(U2/20-24)	mod.										
Uric Acid	II(U2/25-29)											
Calcium Salts	II(U2/30-34)	heavy										
Other	AI(U2/35-39)											
Casts/LPF 100X (Avg/Field)	II(U2/40-44)	0	0	gr. wcd								
RBC/HPF 400X (Avg/Field)	II(U2/45-49)	0-4	0	0-5	3-4	0						
WBC/HPF 400X (Avg/Field)	II(U2/50-54)	3-12	0-4	5-10	4-5	0						
EPITH/HPF 400X (Avg/Field)	II(U2/55-59)	2-5	*	0-2	5-10	3-5						
Mucous	II(U2/60-68)											
Appearance	II(U2/70-80)	yellow	yellow	dk. y	cl. y	cl. y						

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1082F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/8/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>10:00 AM</u>
PATHOLOGY NUMBER	<u>76-2462</u>	DATE KILLED	<u>4/8/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Poor</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>381</u>

SUMMARY:

DRUG INDUCED LESIONS

Omentum; mesentery; peritoneum (SI, spleen, pancreas, liver, LI): +++ fibrous adhesions

Stomach, body-pyloric antrum, fundus: ++ lymphoid hyperplasia

Omentum: ++ focal fibrosis

OBSERVATIONS:

General Examination: The body is that of a female beagle in poor condition. There is a pronounced ocular discharge which is matted on hairless skin near the medial canthus of each eye. There is a pronounced interdigital dermatitis.

Body Cavities and Serosal Surfaces: The abdominal cavity contains approximately 3 cc of red-brown watery fluid. There are extensive fibrous between the omentum, mesentery, stomach and spleen.

Digestive System: The stomach is distorted in shape because of extensive adhesions to the omentum and pancreas. The mucosa in the pyloric antrum and fundic areas shows a slight irregularity in its surface due to discrete nodular elevation approximately 2mm in diameter. Focal areas of the jejunal and ileal mucosa show red discoloration.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible within the mucosa were numerous small to large lymphoid nodules. In addition on the serosal surfaces of the stomach there is thick organized fibrous tissue composed of mature fibroblasts and collagen.

Duodenum: Visible of the serosal surfaces of the duodenum and effecting 30% of its circumference is a thin layer of fibrous tissue. Mature fibroblasts and collagen have been laid down. Otherwise the duodenum is unremarkable.

Jejunum: Visible on the serosal surface of the jejunum and affecting approximately 10% of its circumference is a focus of subserosal hemorrhage and fibrosis. Other than this lesion the jejunum is unremarkable.

Urinary bladder: Visible on the serosal surface of the urinary bladder are focal segments of fibrosis of variable thickness. Small numbers of hemosiderin laden macrophages are present in the fibrous tissue. Otherwise the urinary bladder is unremarkable.

Ileum: Visible on the serosal surface of the ileum and affecting approximately 15% of its circumference is a focal fibrous proliferation. Otherwise the ileum is unremarkable.

Colon: The serosal surface of approximately 25% of the circumference of the colon is covered by a very thick, organized layer of fibrous tissue.

Omentum: Visible within the omental fat are small aggregates of mononuclear cells surrounding small arterioles. Around the margin of the fat there is some increase in fibrous tissue. A few mononuclear inflammatory cells were dispersed in the fibrous tissue.

Cecum: Approximately 75% of the serosal surface of the cecum is covered by fibrous tissue. The fibrous reaction consisted of mature fibroblasts and collagen.

ANIMAL ID: D01083
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 22- 0 29 84 142 262 350

--HEMATOLOGY--

HCT(%)	37	39	41	44	46	53	48
HGB(GZ)	13.0	14.0	13.9	14.7	15.3	16.6	16.7
RBC(10 ¹⁶ /CMM)	4.81	5.37	5.19	5.71	6.37	7.03	6.58
WBC(10 ¹³ /CMM)	10.60	9.68	14.94	13.16	10.02	14.25	14.97
NEUT,I(%)	0.0	0.0	9.0	1.0	0.0	2.0	0.0
NEUT,M(%)	59.0	56.0	55.0	70.0	67.0	71.0	74.0
NEUT,L(%)	6.25	5.42	8.22	9.21	6.71	10.12	11.08
LYMPHO(%)	40.0	40.0	35.0	25.0	29.0	25.0	24.0
LYMPHO(10 ¹³ /CMM)	4.24	3.87	5.23	3.29	2.91	3.56	3.59
MONO(%)	1.0	1.0	0.0	1.0	0.0	0.0	1.0
EOSINO(%)	0.0	3.0	1.0	3.0	4.0	2.0	1.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	0.5	0.1	0.8	1.6	1.1	0.6	2.5
THR(10 ¹⁴ /CMM)	42	25	16	14	16	19	22
PROTIME(SEC)	8.4	9.9	6.4	7.4	7.4	6.9	7.9

--BLOOD CHEM--

BUN(MGZ)	23.2	16.0	12.6	13.6	27.8	22.5	16.5
BS(MGZ)	91	13	85	82	87	79	70
AP(KAU)	16.1	10.2	6.8	4.2	3.6	4.1	3.9
SGOT(RFU/ML)	15	14	14	18	9	11	14
SGPT(RFU/ML)	43	13	13	12	8	7	12
BILI(MGZ)							
CL-(MEQ/L)	115	116	113	112	114	118	118
CA++(MGZ)	9.8	10.2	10.9	10.0	9.6	9.8	10.0
PCO2(MEQ/L)	24.2	25.8	26.8	21.8	25.0	30.4	22.5
PH	7.357	7.322	7.362	7.336	7.389	7.500	7.372
PROTEIN(GZ)	5.80	6.10	5.40				6.30
PCO2(MMHG)	42.7	48.6	46.0	39.4	40.0	38.4	37.4

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1083

Dose Level (Mg/Day): 100

Necropsy Date: 7 April 1976

Day: 380

Sampling Time Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin							
-3	5.2	2.2	3.0	0.706	1.0	0.5	0.6	0.7	0.2	
0	6.1	2.6	3.5	0.745	0.8	1.1	0.7	0.5	0.4	
13	6.6	4.5	2.1	2.158	0.3	0.7	1.0	0.0	0.1	
20	7.2	2.5	4.7	0.545	0.8	1.2	0.5	1.2	1.0	
39	7.0	4.0	3.0	1.333	1.4	0.0	0.9	0.0	0.7	
50	6.6	3.8	2.8	1.360	0.9	0.0	1.5	0.0	0.4	

Tissue HCB (PPM) Level at Necropsy

	Fat	
	<u>Total</u>	<u>Lipid Extract</u>
Bile	22.7	377
		427

URINALYSIS

ANIMAL NUMBER (A/3-10) D1083M
 DAY ONE DATE 032575
 INITIAL BODY WEIGHT 2.3 Kg
 FINAL BODY WEIGHT

COMPOUND HCB
 DOSE 100 mg/dog/day
 ROUTE oral

Treatment Date	A1(A/11-16)	042375061975	081475121275	030976					
Day in Study	I(A/17-19)	29	86	142	263	351			
Sp. Gr.	R(U1/20-24)	1.017	1.065	1.060	1.064	1.052			
pH	R(U1/25-29)	8	8	6	6	6			
Sugar	I(U1/30-34)	0	0	0					
Ketones	I(U1/35-39)	0	0	0					
Blood	I(U1/40-44)	0	0	0					
Protein	I(U1/45-49)	0	1+	1+	1+	1+			

MICROSCOPIC									
Triple Phosphates	I(U2/20-24)	mod.		2+	1+	2+			
Uric Acid	I(U2/25-29)								
Calcium Salts	I(U2/30-34)								
Other	A(U2/35-39)				sperm	sperm			
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy					
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	0	0	0	6-8			
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-4	0	7-10	8-10	2-3			
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-3	3-10	2-5	2-3	6-8			
Mucous	I(U2/60-69)								
Appearance	I(U2/70-80)	yellow	yellow	dk.y	cl.y	cl.y			

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1083M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/7/76</u>
COMPOUND	<u>HCb</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>9:15 AM</u>
PATHOLOGY NUMBER	<u>76-2413</u>	DATE KILLED	<u>4/7/76</u>
SPECIES	<u>Beagle Dogs</u>	PRENECROPSY CONDITION	<u>Fair</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>380</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the pharynx on either side of the laryngeal orifice are 8 nodules each approximately 2.5 mm in diameter. The mucosa of the stomach in the area of the pyloric antrum is covered with approximately 150 similar nodules. Four such nodules are present in the cardia.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum, cardia: Visible in the mucosa were numerous large lymphoid nodules. Some of these were confluent with each other.

ANIMAL ID: D01086
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/05 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 20- 0 29 84 142 262 350

--HEMATOLOGY--

HCT(%)	46	49	47	45	47	50	55
HGB(GZ)	16.1	16.7	15.0	15.7	17.8	17.3	18.8
RBC(10 ¹⁶ /CMH)	6.08	6.84	6.01	6.17	6.76	7.29	7.46
WBC(10 ¹³ /CMH)	7.84	7.83	11.41	11.41	9.14	8.30	10.39
NEUT,I(2WBC)	0.0	0.0	6.0	0.0	0.0	0.0	0.0
NEUT,M(2WBC)	63.0	45.0	50.0	64.0	50.0	61.0	60.0
NEUT,N(10 ¹³)	4.94	3.52	5.71	7.30	4.57	5.06	6.23
LYMPHO(2WBC)	30.0	45.0	31.0	29.0	44.0	24.0	37.0
LYMPHO(10 ¹³)	2.35	3.52	3.54	3.31	4.02	1.99	3.84
MONO(2WBC)	1.0	1.0	3.0	3.0	1.0	10.0	0.0
EOSINO(2WBC)	6.0	9.0	10.0	4.0	5.0	5.0	3.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(2RBC)	1.4	0.3	0.6	0.5	0.8	1.5	0.3
THR(10 ¹⁴ /CMH)	48	37	18	18	27	42	39
PROTIME(SEC)	7.5	8.4	6.4	7.4	7.5	6.9	8.0

--BLOOD CHEM--

BUN(MGX)	12.5	12.0	14.8	12.2	14.4	16.4	10.1
BS(MGX)	86	85	90	78	93	83	70
AP(KAU)	3.9	10.6	3.3	5.1	2.9	4.4	3.1
SGOT(RFU/ML)	15	14	12	15	9	8	13
SGPT(RFU/ML)	10	14	14	12	9	9	8
BILI(MGX)							
CL-(MEQ/L)	116	112	109	110	110	113	111
CA+(MGZ)	10.2	10.6	11.1	10.8	10.8	10.6	10.6
PCO2(MEQ/L)	23.2	25.8	25.0	25.8	23.8	32.8	24.9
PH	7.355	7.313	7.374	7.330	7.374	7.496	7.350
PROTEIN(GZ)	7.00	6.80	6.20				7.30
PCO2(MMHG)	40.3	49.9	41.8	47.6	39.7	41.9	43.9

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1086 Necropsy Date: 6 April 1976
 Dose Level (Mg/Day): 100 Day: 379

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
	Protein	Albumin	Globulin						
-3	7.7	2.9	4.8	0.589	1.4	0.7	1.1	1.0	0.7
0	6.8	2.5	4.3	0.577	1.3	0.9	0.5	1.1	0.4
13	-	-	-	-	-	-	-	-	-
20	7.5	2.8	4.7	0.603	0.9	1.2	0.5	1.1	1.0
39	7.5	4.1	3.4	1.225	0.8	0.0	0.8	1.2	0.7
50	7.9	4.8	3.1	1.525	0.6	0.8	0.8	0.6	0.5

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
81	115

Bile
8.0

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1086F

DAY ONE DATE 032575

INITIAL BODY WEIGHT. 9.3 Kg

FINAL BODY WEIGHT

COMPOUND	HCb	100 mg/dog/day
DOSE		

ROUTE oral

Treatment Date		A1A(U11-16)	042575061975	081475	121275	030976				
Day in Study		I1A(U17-19)	30	86	142	263	351			
Sp. Gr.		RI(U120-24)	1.035	1.040	1.040	1.048	1.023			
pH		RI(U125-29)	6	9	6	6.5	6			
Sugar		I(U130-34)	0	0	0	0	0			
Ketones		I(U135-39)	0	0	0	0	0			
Blood		I(U140-44)	0	0	0	0	0			
Protein		I(U145-49)	trace	1+	trace	1+	trace			
REAGENT STRIP										
MICROSCOPIC										
Triple Phosphates		I(U220-24)			1+					
Uric Acid		I(U225-29)								
Calcium Salts		I(U230-34)	1+				2+			
Other		A(U235-39)				2+	Amph			
Casts/LPF 100X (Avg/Field)		I(U240-44)	WBC	0	waxy					
RBC/HPF 400X (Avg/Field)		I(U245-49)	0	0-5	0-2	1-2	0			
WBC/HPF 400X (Avg/Field)		I(U250-54)	*	*	5-10	6-8	8-10			
EPI TH/HPF 400X (Avg/Field)		I(U255-59)	0-3	1-4	2-6	0-1	2-3			
Mucous		I(U260-69)								
Appearance		I(U270-80)	yellow	yellow	yellow	cl, yk	cl, pl			

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1086F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/6/76</u>
COMPOUND	<u>HCb</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>2:30 PM</u>
PATHOLOGY NUMBER	<u>76-2302</u>	DATE KILLED	<u>4/6/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>379</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum: +++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The mucosa of the stomach in the area of the pyloric antrum is covered by approximately 200-300, 2-3 mm, nodules.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa were numerous small and large lymphoid nodules.

ANIMAL ID: D01091
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 10.00000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/25	4/23	6/17	8/14	12/12	3/09
DAY:	21-	0	29	84	142	262	350
---HEMATOLOGY---							
HCT(%)	39	42	45	45	46	53	49
HGB(GZ)	13.9	15.2	16.8	15.0	15.4	16.8	16.8
RBC(10 ¹⁶ /CMH)	4.61	5.78	5.87	6.09	6.48	7.19	6.70
WBC(10 ¹³ /CMH)	10.38	14.86	10.88	18.65	12.38	12.02	11.69
NEUT,I(%)	0.0	0.0	2.0	0.0	0.0	1.0	0.0
NEUT,M(%)	64.0	75.0	58.0	74.0	56.0	59.0	64.0
NEUT,H(10 ¹³)	6.64	11.15	6.31	13.80	6.93	7.09	7.48
LYMPHO(%)	31.0	22.0	30.0	17.0	32.0	25.0	34.0
LYMPHO(10 ¹³)	3.22	3.27	3.26	3.17	3.96	3.01	3.97
MONO(%)	4.0	2.0	2.0	6.0	2.0	5.0	0.0
EOSINO(%)	1.0	1.0	8.0	3.0	10.0	10.0	2.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	1.2	0.6	0.9	0.9	0.7	0.4	0.9
THR(10 ¹⁴ /CMH)	28	19	23	11	18	26	29
PROTIME(SEC)	5.9	7.9	6.4	6.4	7.4	7.4	7.9

---BLOOD CHEM---

BUN(MGX)	16.2	11.0	19.7	11.8	18.7	19.8	15.4
BS(MGX)	74	66	81	62	78	78	68
AP(KAU)	5.2	9.8	4.5	2.9	2.2	1.8	2.2
SGOT(RFU/ML)	16	15	15	13	9	10	13
SGPT(RFU/ML)	15	15	15	11	9	9	9
BILI(MGX)							
CL-(MEQ/L)	116	111	110	114	113	116	117
CA++(MGZ)	9.6	9.8	11.1	10.0	10.6	9.8	10.4
PCO2(MEQ/L)	24.2	21.6	28.0	26.2	28.0	30.8	25.6
PH	7.307	7.246	7.345	7.264	7.332	7.410	7.328
PROTEIN(GZ)	6.00	6.60	5.60	56.8	51.6	47.5	6.80
PCO2(MMHG)	47.7	47.9	50.7				47.3

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1091 Necropsy Date: 6 April 1976
Dose Level (Mg/Day): 100 Day: 377

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	7.1	3.2	3.9	0.822	1.0	1.0	0.7	0.7	0.5
0	6.6	2.6	4.0	0.638	1.3	1.0	1.1	0.4	0.3
13	-	-	-	-	-	-	-	-	-
20	7.0	2.5	4.5	0.570	0.9	1.2	0.7	0.8	0.9
39	6.5	3.7	2.8	1.289	1.2	0.0	1.1	0.0	0.5
50	7.3	4.8	2.5	1.906	0.7	0.0	0.5	0.9	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Total</u>
16.2	229
	254

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1091M
DAY ONE DATE		032575
INITIAL BODY WEIGHT		9.2 Kg
FINAL BODY WEIGHT		

COMPOUND	HCb
DOSE	100 mg/dog/day
ROUTE	oral

Treatment Date		A(U/11-16)	042375061975081475	121275	030974
Day in Study		I(U/17-19)	29	86	142
Sp. Gr.		R(U1/20-24)	1.056	1.045	1.040
pH		R(U1/25-29)	9	6	6
Sugar		I(U1/30-34)	0	0	0
Ketones		I(U1/35-39)	0	0	0
Blood		I(U1/40-44)	0	0	0
Protein		I(U1/45-49)	1+	1+	1+

MICROSCOPIC		light	2+	3+
Triple Phosphates		light		
Uric Acid				
Calcium Salts		light		1+
Other				sperm
Casts/LPF 100X (Avg/Field)		0	gran.	few
RBC/HPF 400X (Avg/Field)		0	0	0-1
WBC/HPF 400X (Avg/Field)		0-2	0-3	0
EPITH/HPF 400X (Avg/Field)		0-2	0-3	0-1
Mucous				3-5
Appearance		yellow	yellow/dk.y	cl y

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1091M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/6/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>10:15 AM</u>
PATHOLOGY NUMBER	<u>76-2301</u>	DATE KILLED	<u>4/6/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>377</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, fundus, pyloric antrum: +++ lymphoid hyperplasia

Omentum-ceacum: + focal fibrous adhesion

OBSERVATIONS:

Digestive System: The mucosa of the stomach in the areas of the pyloric antrum, fundus and cardia was covered with approximately 500, 2-3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa were numerous large and confluent lymphoid nodules.

ANIMAL ID: D01102
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 4
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/06 3/25 4/23 6/17 8/14 12/12 1/16
 DAY: 19- 0 29 84 142 262 297

--HEMATOLOGY--

HCT(%)	43	43	39	50	46	46	32
HGB(GZ)	15.5	15.7	14.7	17.3	14.9	14.2	11.8
RBC(10 ¹⁶ /CHM)	5.56	5.93	5.55	6.42	6.54	6.18	4.33
WBC(10 ¹³ /CHM)	11.21	14.72	14.68	16.92	25.22	25.57	56.29
NEUT,I(ZWBC)	1.0	0.0	4.0	0.0	0.0	1.0	15.0
NEUT,M(ZWBC)	50.0	57.0	55.0	64.0	77.0	77.0	66.0
NEUT,L(ZWBC)	5.61	8.39	8.07	10.83	19.42	19.69	37.15
LYMPHO(ZWBC)	42.0	39.0	30.0	26.0	19.0	17.0	16.0
LYMPHO(10 ¹³)	4.71	5.74	4.40	4.40	4.79	4.35	9.01
MONO(ZWBC)	3.0	2.0	0.0	6.0	3.0	4.0	0.0
EOSINO(ZWBC)	4.0	2.0	11.0	4.0	1.0	1.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORML(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.8	0.3	0.0	2.2	0.3	0.4	0.2
THR(10 ¹⁴ /CHM)	30	38	21	32	29	29	44
PROTIME(SEC)	7.4	7.5	6.4	6.4	6.9	6.9	

--BLOOD CHEM--

BUN(MGZ)	17.0	17.0	14.8	18.9	15.3	14.4	18.4
BS(MGZ)	75	77	92	90	79	58	18
AP(KAU)	4.8	10.2	3.5	3.6	6.5	7.1	70.4
SGOT(RFU/ML)	11	11	13	12	10	13	70
SGPT(RFU/ML)	20	14	15	9	10	9	25
BILI(MGZ)							
CL-(MEQ/L)	113	117	115	114	113	116	110
CA++(MGZ)	10.2	10.2	10.0	9.4	10.4	9.4	7.6
PCO2(MEQ/L)	23.2	25.0	27.2	21.8	26.8	26.8	
PH	7.300	7.349	7.360	7.225	7.315	7.390	
PROTEIN(GZ)	7.00	6.20	5.80				
PCO2(MMHG)	45.8	44.0	47.6	51.0	51.6	43.1	

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1102 Necropsy Date: 16 January 1976
 Dose Level (Mg/Day): 100 Day: 298

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				
	Protein	Albumin	Globulin		α -1	α -2	β -1	β -2
-3	6.6	2.4	4.2	0.554	1.1	0.7	0.8	0.9
0	6.2	3.1	3.1	1.014	0.7	0.8	0.7	0.6
13	-	-	-	-	-	-	-	-
20	7.9	2.6	5.3	0.492	1.1	1.6	0.5	1.2
39	6.2	1.9	4.3	0.437	0.5	1.4	1.8	0.0
50				Died				

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
2680	13692

Bile
274

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1102F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>1/16/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>-</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>9:00 PM</u>
PATHOLOGY NUMBER	<u>76-25</u>	DATE KILLED	<u>1/15/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Poor</u>
AGE	<u>19 mo</u>	POSTMORTEM STATE	<u>Fair</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>298</u>

SUMMARY:

DRUG INDUCED LESIONS

Omentum: +++ fat atrophy; + focal fibrosis; ++ subacute steatitis

Liver: ++ subacute hepatitis; ++ bile duct hyperplasia; ++ chronic pericholangitis; (+) fatty change

Rectum: +++ focal serosal fibrosis

Lungs: ++ focal bronchopneumonia

Lymphoid Tissues: + to +++ atrophy (thymus, +, superficial and mandibular cervical lymph nodes, spleen, tonsils, colon, rectum, ileum)

Tonsils: (+) focal necrosis

OBSERVATIONS:

General Examination: The body is that of a small emaciated, severely dehydrated female beagle. At the medial canthus of each eye, there is much crusty material on the hair from a chronic ocular discharge. In the left foreleg an intravenous cannula is introduced. Approximately 100 cc of lactated ringers was given intravenously shortly before death. The rib cage is very prominent; there is generalized muscular atrophy; the temporal muscles are sunken and the zygomatic arch is prominent. All muscle groups are small.

Body Cavities and Serosal Surfaces: The omentum is reduced to a small flap approximately 7 x 3 cm in size attached to the greater curvature of the stomach. There is very, very little body fat or perirenal fat. Within the abdominal cavity is 5 cc of semiopaque amber colored fluid. The tissues in the anterior mediastinum in the area of the thymus appear to be gelatinous. The thymus was difficult to visualize. The left horn of the uterus and the left broad ligament is tightly adherent by fibrous adhesions to the descending colon. This appears to be a long standing lesion. In addition, the tail of pancreas is tightly adherent to the serosal surface of the ileocecal colic portion of the bowel. Blood vessels in the mesentery and the GI tract are engorged with blood.

Respiratory System: The ventral aspect of the left apical of the lobe shows an irregular pattern of slightly firm dark purple-red light brown areas of discoloration. The apical lobe on the same side appears to be slightly emphysematous.

Cardiovascular System: On the anterior epicardial surface of the right ventricle near the interventricular septum is a focal gray-tan slightly raised area approximately 6 mm in diameter which appears to be organized fibrin. There are about 4 cc of clear amber colored fluid in the pericardial sac.

Hemic and Lymphatic System: The spleen is small and the edges are sharp. The pericapsular tissues around the mesenteric lymph nodes are moist and gelatinous. Visible from the capsular surface of the left tonsil is a focal red area about 5 mm x 3 mm.

Digestive System: The serosal surface of the stomach and the intestines is pale gray. The liver has a nutmeg pattern with yellow mottling. It appears to be larger and more friable than usual. On section it is a uniform gray-tan.

MICROSCOPIC OBSERVATIONS:

Lungs: Capillaries throughout the lungs are very congested. In focal areas, there is an acute broncho pneumonia. Bronchioles and alveoli are filled with polymorphonuclear leukocytes and edema. The pneumonic area of the lung is restricted to one lobe.

Liver: Hepatocytes throughout the liver show a slight fatty change. There is a moderate increase in bile ducts throughout the liver and a moderate increase in connective tissues surrounding these bile ducts. The epithelium lining the ducts, in some cases, is atypical. In addition, there are moderate numbers of mononuclear inflammatory cells including lymphocytes and plasma cells surrounding central veins scattered about within the parenchyma. Overall, this appears to be a subacute hepatitis with chronic pericholangitis, and bile duct hyperplasia.

Tonsils: The tonsils are moderately atrophic and show slight necrosis.

Tracheal lymph node: The tracheal node is slightly less cellular than normal.

Mesenteric lymph node: The node is slightly less cellular than normal.

Superficial cervical lymph node: The node is slightly less cellular than normal.

Thymus: The thymus shows moderate atrophy.

Ileum: +++ lymphoid atrophy

Spleen: ++ atrophy. There are moderate numbers of hemosiderin laden macrophages throughout the red pulp.

Mandibular lymph node: ++ atrophy. In addition there was focal cortical hemorrhage and accumulation of hemosiderin laden macrophages.

Colon: ++ lymphoid atrophy.

Rectum: ++ lymphoid atrophy and serosal fibrosis. On the serosa there is pronounced fibrosis. Small numbers of mononuclear and polymorphonuclear leukocytes are present in the fibrous tissue.

Omental fat: The omental fat is very condensed. It shows slight fibrosis and moderate numbers of acute and subacute inflammatory cells dispersed throughout.

ANIMAL ID: D01110
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/25/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 10.000000
 (MG/DOG): 100.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/06 3/25 4/23 6/17 8/14 12/12 3/09
 DAY: 19- 0 29 84 142 262 350

--HEMATOLOGY--

HCT(%)	43	46	43	53	48	49	49
HGB(GZ)	15.6	16.5	15.9	18.1	15.9	17.2	16.9
RBC(10 ¹⁶ /CMH)	6.12	6.81	6.50	7.05	6.73	7.18	6.88
WBC(10 ¹³ /CMH)	9.42	10.16	9.27	11.77	12.10	13.53	18.33
NEUT,I(%)WBC)	0.0	0.0	3.0	0.0	0.0	0.0	1.0
NEUT,M(%)WBC)	59.0	45.0	43.0	66.0	49.0	53.0	64.0
NEUT,M(10 ¹³)	5.56	4.57	3.99	7.77	5.93	7.17	11.73
LYMPHO(%)WBC)	37.0	49.0	47.0	27.0	48.0	42.0	33.0
LYMPHO(10 ¹³)	3.49	4.98	4.36	3.18	5.81	5.68	6.05
MONO(%)WBC)	2.0	1.0	5.0	3.0	0.0	2.0	1.0
EOSINO(%)WBC)	2.0	5.0	2.0	4.0	3.0	3.0	1.0
BASO(%)WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%)WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	0.8	0.5	0.5	1.2	0.2	0.5	0.5
THR(10 ¹⁴ /CMH)	22	46	13	20	23	20	19
PROTIME(SEC)	7.5	7.9	6.8	7.0	7.9	6.9	7.9

--BLOOD CHEM--

BUN(MGZ)	18.5	10.0	14.1	15.2	15.4	12.3	10.3
BS(MGZ)	80	74	91	86	87	88	70
AP(KAU)	3.9	10.4	3.7	4.1	5.0	3.9	3.9
SGOT(RFU/ML)	15	15	15	20	11	12	14
SGPT(RFU/ML)	15	14	15	16	9	9	10
BILI(MGZ)							
CL-(MEQ/L)	113	110	111	112	111	114	116
CA++(MGZ)	10.0	10.4	10.4	10.0	10.0	10.6	10.0
PCO2(MEQ/L)	24.0	24.8	27.0	20.8	26.0	31.0	22.0
PH	7.305	7.298	7.357	7.320	7.302	7.442	7.310
PROTEIN(GZ)	6.80	6.30	6.00	38.8	51.2	44.6	7.10
PCO2(MMHG)	46.8	49.0	47.1				42.2

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1110 Necropsy Date: 7 April 1976
 Dose Level (Mg/Day): 100 Day: 380

Sampling Time Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
		Albumin	Globulin						
-3	7.7	2.7	5.0	0.544	1.5	0.7	0.8	1.2	0.8
0	6.3	2.8	3.5	0.800	0.7	0.8	0.9	0.8	0.3
13	-	-	-	-	-	-	-	-	-
20	7.8	3.1	4.7	0.643	0.9	1.2	0.8	0.7	1.1
39	7.7	4.0	3.7	1.074	0.7	0.9	0.8	1.0	0.4
50	7.9	4.3	3.6	1.205	0.7	0.9	0.6	0.9	0.4

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
11.3	202	295

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1110F
DAY ONE DATE		032575
INITIAL BODY WEIGHT		7.7 Kg
FINAL BODY WEIGHT		

COMPOUND		HCR
DOSE		100 mg/dog/day
ROUTE		oral

Treatment Date		A(U1/1-16)	042375	062075	081475	121275	030976				
Day in Study		I(U1/17-19)	29	87	142	263	351				
Sp. Gr.		R(U1/20-24)	1.035	1.055	1.070	1.064	1.068				
pH		R(U1/25-29)	6	6	6	6	6				
Sugar		I(U1/30-34)	0	0	0	0	0				
Ketones		I(U1/35-39)	0	0	0	0	0				
Blood		I(U1/40-44)	0	0	0	0	trace				
Protein		I(U1/45-49)	0	1+	1+	1+	1+				

MICROSCOPIC		I(U2/20-24)	I(U2/25-29)	I(U2/30-34)	I(U2/35-39)	I(U2/40-44)	I(U2/45-49)	I(U2/50-54)	I(U2/55-59)	I(U2/60-69)	I(U2/70-80)
Triple Phosphates				2+							
Uric Acid											
Calcium Salts				2+							
Other											
Casts/LPF 100X (Avg/Field)						0	waxy	waxy			
RBC/HPF 400X (Avg/Field)						0	0	0	0-1	10-15	
WBC/HPF 400X (Avg/Field)						2-5	5-10	5-10	5-10	3-5	
EPITH/HPF 400X (Avg/Field)						0-2	5-10	*	10-15	6-8	
Mucous											
Appearance						yellow	yb	dk y	amber	cl dk y	

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1110F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/25/75</u>	NECROPSY DATE	<u>4/7/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>100</u>	HOUR DIED	<u>2:00 PM</u>
PATHOLOGY NUMBER	<u>76-2412</u>	DATE KILLED	<u>4/7/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>380</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, fundus, pyloric antrum and canal: +++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The mucosa of the stomach in the areas of the fundus, pyloric antrum and pyloric canal are covered with numerous 2-4 mm nodules giving the lining a granular appearance.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum, fundus: Visible in the mucosa are numerous small to large, sometimes confluent lymphoid nodules.

ANIMAL ID: D01080
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 10
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/05 3/26 4/24 6/18 8/15
 DAY: 22- 0 29 84 142

--HEMATOLOGY--

HCT(%)	46	51	46	55	46
HGB(GZ)	16.5	17.8	17.8	17.8	17.7
RBC(10 ⁶ /CMH)	6.38	6.89	6.85	7.04	6.93
WBC(10 ³ /CMH)	9.23	9.75	13.71	11.74	9.47
NEUT,I(ZWBC)	0.0	0.0	3.0	0.0	0.0
NEUT,M(ZWBC)	68.0	55.0	57.0	57.0	52.0
NEUT,H(10 ³)	6.28	5.36	7.81	6.69	4.92
LYMPHO(ZWBC)	20.0	31.0	29.0	37.0	32.0
LYMPHO(10 ³)	1.85	3.02	3.98	4.34	3.03
MONO(ZWBC)	6.0	3.0	3.0	3.0	4.0
EOSINO(ZWBC)	6.0	11.0	7.0	3.0	12.0
BASO(ZWBC)	0.0	0.0	1.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.6	0.7	0.2	0.4	0.5
THR(10 ⁴ /CMH)	31	18	34	30	12
PROTIME(SEC)	7.4	8.4	6.4	9.9	7.9

--BLOOD CHEM--

BUN(MGX)	18.6	18.8	17.2	19.5	16.7
BS(MGX)	76	72	73	64	83
AP(KAU)	2.6	3.6	5.1	3.6	3.1
SGOT(RFU/ML)	15	18	10	10	12
SGPT(RFU/ML)	18	17	12	16	12
BILI(MGX)					
CL-(MEQ/L)	117	112	112	111	112
CA++(MGX)	10.2	10.2	10.0	10.2	10.4
PCO2(MEQ/L)	23.8	28.5	27.2	26.8	26.8
PH	7.312	7.328	7.334	7.314	7.374
PROTEIN(GZ)	7.00	5.70	5.80		
PCO2(MMHG)	45.7	53.1	50.2	51.4	44.4

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1080 Necropsy Date: 20 August 1975
 Dose Level (Mg/Day): 10 Day: 148

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.6	2.6	4.0	0.649	1.3	0.9	0.7	0.6	0.5
0	5.7	2.5	3.2	0.771	0.9	0.8	0.5	0.6	0.4
13	-	-	-	-	-	-	-	-	-
20	7.3	3.5	3.8	0.897	0.8	1.0	0.5	0.8	0.7
39									
50									

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Sacrificed

Tissue HCB (PPM) Level at Necropsy

	Fat	
	<u>Total</u>	<u>Lipid Extract</u>
<u>Bile</u>		
1.9	70.9	90.8

URINALYSIS

ANIMAL NUMBER (A/3-10) D1080F
 DAY ONE DATE 032675
 INITIAL BODY WEIGHT 8.4 Kg
 FINAL BODY WEIGHT
 COMPOUND HCB
 DOSE 10 mg/dog/day
 ROUTE oral

Treatment Date		A1A/11-16		042475062075081975																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																											
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* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1080F</u>	NECROPSY DATE	<u>8/20/75</u>
DAY ONE DATE	<u>3/26/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>1:30 PM</u>
DOSE Mg/Da	<u>10</u>	DATE DIED	<u>8/20/75</u>
PATHOLOGY NUMBER	<u>75-6080</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>148</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach: pyloric antrum, + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the esophagus at the junction with the epiglottis there is a single, focal slightly raised 3 mm nodule. In the cardia of the stomach at the junction with the esophagus there is a linear distribution of 10 slightly raised 3-4 mm nodules. In the mucosa of stomach in the region of the pyloric antrum and extending into the body there are many slightly raised 3-4 mm nodules. The fundic region reveals only a rare nodule. At the base of the tongue in the mucosa there are approximately 10-15 slightly raised circular nodules about 3-4 mm in diameter. Microscopically pyloric and antral mucosa contain numerous lymphoid nodules of small to moderate size.

MICROSCOPIC OBSERVATIONS:

Stomach: In the mucosa of the pyloric antrum there are numerous small to medium sized lymphoid nodules.

ANIMAL ID: D01125
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

1.000000
 10.00000

SCHEDULE: DAILY FOR TWELVE MONTHS

NO GRADES

DATE: 3/18 3/26 4/24 6/18 8/15
 DAY: 8- 0 29 84 142

--HEMATOLOGY--

HCT(%)	50	42	46	46	44
HGB(GZ)	17.5	16.0	16.7	15.6	14.9
RBC(10 ¹² /CMM)	6.51	5.88	6.21	6.35	6.11
WBC(10 ³ /CMM)	13.44	11.96	10.56	14.47	10.13
NEUT(I(ZWBC)	0.0	0.0	0.0	0.0	1.0
NEUT(M(ZWBC)	59.0	61.0	56.0	51.0	43.0
NEUT(M(10 ¹³)	7.93	7.30	5.91	7.38	4.36
LYMPHO(ZWBC)	32.0	33.0	24.0	44.0	43.0
LYMPHO(10 ¹³)	4.30	3.95	2.53	6.37	4.36
MONO(ZWBC)	2.0	3.0	3.0	2.0	0.0
EOSINO(ZWBC)	7.0	3.0	7.0	3.0	13.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.7	0.2	0.8	0.2	0.3
THR(10 ¹⁴ /CMM)	21	36	33	25	22
PROTIME(SEC)	9.4	8.4	6.6	10.0	8.4

--BLOOD CHEM--

BUN(MGZ)	15.4	16.5	12.2	21.1	15.6
BS(MGZ)	92	83	97	95	92
AP(KAU)	3.3	3.1	4.9	2.9	2.2
SGOT(RFU/ML)	17	19	16	17	9
SGPT(RFU/ML)	15	16	12	13	8
BILI(MGZ)					
CL-(MEQ/L)	116	114	114	113	107
CA++(MGZ)	10.6	10.4	10.2	10.0	10.6
PCO2(MEQ/L)	24.0	26.2	23.4	24.2	26.6
PH	7.262	7.354	7.391	7.302	7.354
PROTEIN(GZ)	6.00	6.20	6.40		
PCO2(MMHG)	51.9	46.1	37.6	47.5	46.5

Serum Electrophoresis

(All Values = gm %)

Necropsy Date: 19 August 1975
Day: 147

Dog No.: 1125
Dose Level (Mg/Day): 10

Sampling Time Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
		Albumin	Globulin							
-3	-	-	-	-	-	-	-	-	-	-
0	6.2	2.9	3.3	0.864	0.7	0.9	0.5	0.7	0.6	0.6
13	-	-	-	-	-	-	-	-	-	-
20	7.5	3.1	4.4	0.690	0.8	1.4	0.6	0.5	1.1	1.1
39				Sacrificed						
50										

Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Total</u>	<u>Lipid Extract</u>
21.3	30.4

Bile
0.78

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1125M</u>	NECROPSY DATE	<u>8/19/75</u>
DAY ONE DATE	<u>3/26/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:30 AM</u>
DOSE Mg/Da	<u>10</u>	DATE DIED	<u>8/19/75</u>
PATHOLOGY NUMBER	<u>75-6077</u>	PRENECROPSY CONDITION	<u>Good</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OR NECROPSY			<u>147</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach: fundus, + lymphoid hyperplasia

Colon: ? + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the stomach at the region of the pyloric antrum is a small area composed of slightly raised coalesced nodules which measure 3 to 4 mm in diameter. The extent of this lesion is less than that observed in the other HCB dogs thus far. The fundic area of the stomach, the esophagus and epiglottis are free of lymphoid nodules. At the base of the tongue there are 15 to 20 slightly raised 2 to 3 mm gray-tan nodules in the mucosa. In the mucosa of the caecum there is a single large nodule approximately 9 mm in diameter. The central area of this nodule is reddened. Smaller nodules with a slight dimple in the center are visible in the mucosa. There are about 5 to 6 mm in diameter and rise approximately 1 mm.

ANIMAL ID: D01094
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/26 4/24 6/18 8/15
 DAY: 22- 0 29 84 142

---HEMATOLOGY---

HCT(%)	45	47	45	48	45
HGB(GZ)	16.5	16.6	16.9	16.6	17.0
RBC(10 ¹⁶ /CMH)	6.01	6.46	6.68	6.59	6.78
WBC(10 ¹³ /CMH)	9.10	9.90	10.19	10.10	9.31
NEUT,I(ZWBC)	0.0	0.0	1.0	0.0	0.0
NEUT,M(ZWBC)	68.0	55.0	54.0	56.0	64.0
NEUT,M(10 ¹³)	6.19	5.45	5.50	5.66	5.96
LYMPHO(ZWBC)	29.0	35.0	32.0	35.0	30.0
LYMPHO(10 ¹³)	2.64	3.47	3.26	3.54	2.79
MONO(ZWBC)	0.0	1.0	3.0	1.0	2.0
EOSINO(ZWBC)	3.0	9.0	10.0	8.0	4.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	2.0	0.8	0.2	0.7	1.4
THR(10 ¹⁴ /CMH)	29	19	44	34	18
PROTIME(SEC)	5.9	8.4	6.4	9.9	8.4

---BLOOD CHEM---

BUN(MGZ)	13.5	11.7	13.0	21.7	14.8
BS(MGZ)	53	99	75	79	103
AP(KAU)	4.5	4.2	4.0	2.8	1.9
SGOT(RFU/ML)	18	22	10	12	8
SGPT(RFU/ML)	26	75	15	15	15
BILI(MGZ)					
CL-(MEQ/L)	119	112	114	113	110
CA++(MGZ)	10.4	10.7	10.2	9.8	10.2
PCO2(MEQ/L)	21.8	26.2	25.5	23.8	24.0
PH	7.362	7.340	7.395	7.311	7.425
PROTEIN(GZ)	6.20	5.90	6.00		
PCO2(MMHG)	36.7	47.7	40.4	45.6	35.3

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1094 Necropsy Date: 19 August 1975
 Dose Level (Mg/Day): 10 Day: 147

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	7.2	3.2	4.0	0.819	1.3	0.9	0.6	0.8	0.4
0	5.9	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-
20	7.0	3.0	4.0	0.759	0.7	1.0	0.3	0.8	1.1
39									
50									

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Tissue HCB (PPM) Level at Necropsy

Fat	
Bile	Lipid Extract
3.8	78.8
	156

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1094F
DAY ONE DATE		032675
INITIAL BODY WEIGHT		8.0 Kg
FINAL BODY WEIGHT		

COMPOUND	HCBCB
DOSE	10 mg/dog/day
ROUTE	oral

[illegible]

Too numerous to count

NECROPSY AND PATHOLOGY REPORTS

ANIMAL NUMBER	<u>D1094F</u>	NECROPSY DATE	<u>8/19/75</u>
DAY ONE DATE	<u>3/26/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>9:30 AM</u>
DOSE Mg/Da	<u>10</u>	DATE DIED	<u>8/19/75</u>
PATHOLOGY NUMBER	<u>75-6076</u>	PRENECROPSY CONDITION	<u>Fair</u>
SPECIED	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>147</u>

SUMMARY:

DRUG INDUCED LESIONS

Esophagus: posterior end, (+) focal lymphoid hyperplasia

Stomach: fundus, pyloric antrum, +++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: Visible in the mucosa of the esophagus at the epiglottal-esophageal and esophageal-cardiac junctions are 3 mm slightly raised gray nodules. Similar nodules are in the mucosa of the stomach. The numbers of nodules increase in the fundic region of the stomach. Some dispersed nodules are visible along the lesser curvature of the stomach. These nodules are isolated. In the pyloric antrum there are slightly raised 3-4 mm coalescent nodules. In the mucosa of the caecum there are many nodules approximately 5 mm in diameter.

MICROSCOPIC OBSERVATIONS:

Stomach: In the mucosa of the fundus and pyloric antrum there are numerous large nodules all

of which have germinal centers. The lymphoid nodules in the body of the stomach are small and inconspicuous.

ANIMAL ID: D01117
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/17 3/26 4/24 6/18 8/15
 DAY: 9- 0 29 84 142

---HEMATOLOGY---

HCT(%)	51	46	49	47	49
HGB(G%)	16.4	17.0	16.9	16.2	16.5
RBC(10 ¹⁶ /CMH)	6.76	6.41	6.76	6.60	7.34
WBC(10 ¹³ /CMH)	9.91	11.82	10.01	11.18	9.59
NEUT,I(%)	0.0	0.0	1.0	0.0	1.0
NEUT,M(%)	67.0	65.0	72.0	65.0	68.0
NEUT,H(%)	6.64	7.68	7.21	7.27	6.52
LYMPHO(%)	23.0	32.0	15.0	34.0	28.0
LYMPHO(10 ¹³ /CMH)	2.28	3.78	1.50	3.80	2.69
MONO(%)	2.0	2.0	2.0	1.0	0.0
EOSINO(%)	8.0	1.0	10.0	0.0	3.0
BASO(%)	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0
RET(%)	0.2	0.6	0.3	0.5	1.0
THR(10 ¹⁴ /CMH)	26	19	18	21	12
PROTIME(SEC)	6.4	7.9	6.4	10.5	7.4

---BLOOD CHEM---

BUN(MG%)	16.1	20.1	21.7	24.6	20.5
BS(MG%)	92	97	95	81	98
AP(KAU)	4.4	4.2	5.0	5.2	2.1
SGOT(RFU/ML)	17	17	13	13	11
SGPT(RFU/ML)	16	16	12	14	8
BILI(MG%)					
CL-(MEQ/L)	118	113	117	115	115
CA++(MG%)	11.3	10.9	10.4	9.8	9.8
PCO2(MEQ/L)	22.2	26.0	24.8	24.0	23.0
PH	7.334	7.362	7.393	7.385	7.390
PROTEIN(G%)	6.10	5.80	5.80		
PCO2(MMHG)	40.3	44.3	39.3	39.0	36.8

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1117

Dose Level (Mg/Day): 10

Necropsy Date: 15 August 1975

Day: 143

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	5.8	2.6	3.2	0.810	0.8	0.7	0.5	0.6	0.5
13	-	-	-	-	-	-	-	-	-
20	7.4	2.8	4.6	0.620	0.7	1.3	0.5	0.9	1.1
39									
50									

Sacrificed

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
106	144

Bile
3.6

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1117M</u>	NECROPSY DATE	<u>8/15/75</u>
DAY ONE DATE	<u>3/26/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>9:00 AM</u>
DOSE Mg/Da	<u>10</u>	DATE DIED	<u>8/15/75</u>
PATHOLOGY NUMBER	<u>75-5992</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>10 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>143</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach: fundus, pyloric antrum, + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the fundic region of the stomach near the esophago-cardiac junction, there is a suggestion of slight nodules in the mucosa. These are coalescent and approximately 2-4 mm in diameter. A similar 2 cm wide band is noted at the junction of the body and pyloric antrum. This is studded with numerous single and coalescent 3-4 mm, slightly raised white-grey nodules. Individual nodules are prominent in the pyloric area. The mucosa of the esophagus is unremarkable.

MICROSCOPIC OBSERVATIONS:

Stomach: In the mucosa of the fundus and pyloric antrum there are numerous lymphoid nodules many of which have active germinal centers. A few very small lymphoid nodules are visible in the body.

MICROSCOPIC OBSERVATIONS:

Colon: Within the submucosa of the colon is an extremely large lymphoid nodule, much larger than normally present. A few smaller lymphoid nodules are also present.

Stomach: In the mucosa of the lamina propria there are numerous lymphoid nodules.

ANIMAL ID: D01071
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 10
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL
 TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS
 ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/26 4/24 6/18 8/15 12/15 3/08
 DAY: 25- 2- 27 82 140 262 346

--HEMATOLOGY--

HCT(Z)	45	43	43	48	48	47	45
HGB(GZ)	15.9	15.4	15.7	16.3	17.4	18.0	16.8
RBC(10 ¹⁶ /CMM)	6.28	6.28	6.26	6.71	6.89	6.87	7.12
WBC(10 ¹³ /CMM)	9.90	11.21	10.38	11.25	11.03	11.44	12.03
NEUT,I(ZWBC)	0.0	0.0	6.0	0.0	0.0	5.0	2.0
NEUT,M(ZWBC)	59.0	55.0	48.0	25.0	59.0	58.0	51.0
NEUT,M(10 ¹³)	5.84	6.17	4.98	2.81	6.51	6.64	6.14
LYMPHO(ZWBC)	34.0	44.0	36.0	70.0	40.0	29.0	36.0
LYMPHO(10 ¹³)	3.37	4.93	3.74	7.88	4.41	3.32	4.33
MONO(ZWBC)	3.0	0.0	4.0	2.0	1.0	2.0	3.0
EOSINO(ZWBC)	4.0	1.0	6.0	3.0	0.0	6.0	8.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.7	0.4	0.2	0.6	1.5	0.6	0.7
THR(10 ¹⁴ /CMM)	31	22	14	25	21	17	22
PROTIME(SEC)	7.5	10.4	7.4	11.4	9.0	6.9	8.4

--BLOOD CHEM--

BUN(MGZ)	10.4	16.2	14.2	15.2	12.5	16.6	16.1
BS(MGZ)	85	83	77	67	88	74	78
AP(KAU)	1.9	3.0	3.6	2.2	2.1	1.5	2.2
SGOT(RFU/ML)	15	16	9	18	11	10	11
SGPT(RFU/ML)	15	14	10	15	12	12	12
BILI(MGZ)							
CL-(MEQ/L)	115	114	110	115	105	113	115
CA++(MGZ)	10.2	9.8	10.4	10.8	10.0	11.2	10.4
PCO2(MEQ/L)	22.2	24.8	25.2	21.2	25.8	18.0	22.0
PH	7.347	7.354	7.347	7.312	7.398	7.312	7.298
PROTEIN(GZ)	6.80	6.20	6.20	40.9	40.6	34.0	7.10
PCO2(MMHG)	39.2	43.1	45.0	40.9	40.6	34.0	43.4

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1071

Dose Level (Mg/Day): 10

Necropsy Date: 2 April 1976

Day: 374

Total

Sampling Time (Weeks)	Protein	Albumin	Globulin	Albumin/Globulin (Ratio)	<u>α-1</u>	<u>α-2</u>	<u>β-1</u>	<u>β-2</u>	<u>γ</u>
-3	7.3	2.9	4.4	0.643	1.1	0.9	1.0	0.7	0.6
0	6.2	2.6	3.6	0.735	0.8	0.9	0.8	0.7	0.4
13	6.7	5.3	1.4	3.818	0.1	0.1	0.5	0.0	0.6
20	8.1	3.4	4.7	0.740	1.1	1.2	0.4	1.2	0.8
39	7.3	4.3	3.0	1.438	0.6	0.7	0.6	1.0	0.2
50	7.2	4.9	2.3	2.146	0.2	0.5	0.6	0.6	0.4

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	<u>Total</u>	<u>Lipid Extract</u>
2.70	41	50

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1071M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>4/2/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>9:20 AM</u>
PATHOLOGY NUMBER	<u>76-2237</u>	DATE KILLED	<u>4/2/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>374</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: +++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the gastric mucosa of the pyloric antrum are approximately 400 to 500 2-3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa of the stomach are numerous lymphoid nodules.

ANIMAL ID: D01074
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/03	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	23-	0	29	84	142	264	348
--HEMATOLOGY--							
HCT(%)	54	55	54	53	52	47	54
HGB(GZ)	19.5	19.9	20.6	16.3	19.5	18.5	20.6
RBC(10 ¹⁶ /CMH)	7.08	7.67	7.32	6.60	7.25	6.82	8.04
WBC(10 ¹³ /CMH)	9.37	7.76	7.93	12.03	8.70	7.69	9.57
NEUT,I(XWBC)	0.0	0.0	7.0	0.0	0.0	2.0	1.0
NEUT,M(XWBC)	74.0	56.0	46.0	35.0	70.0	62.0	61.0
NEUT,H(10 ¹³)	6.93	4.35	3.65	4.21	6.09	4.77	5.84
LYMPHO(XWBC)	23.0	31.0	37.0	55.0	23.0	32.0	26.0
LYMPHO(10 ¹³)	2.16	2.41	2.93	6.62	2.00	2.46	2.49
MONO(XWBC)	3.0	3.0	6.0	6.0	1.0	2.0	5.0
EOSINO(XWBC)	0.0	10.0	4.0	4.0	6.0	2.0	7.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	0.9	1.0	0.3	0.4	1.3	0.3	1.0
THR(10 ¹⁴ /CMH)	28	18	18	13	15	23	46
PROTIME(SEC)	8.9	9.0	7.9	10.5	8.4	6.4	7.4

--BLOOD CHEM--

BUN(MGZ)	15.8	17.1	15.6	19.0	14.2	14.6	21.2
BS(MGZ)	110	92	83	75	87	67	66
AP(KAU)	4.4	3.1	3.3	3.3	2.9	3.6	2.1
SGOT(RFU/ML)	17	16	9	15	7	9	18
SGPT(RFU/ML)	31	11	11	13	8	9	12
BILI(MGZ)							
CL-(MEQ/L)	116		110	110	108	114	117
CA++(MGZ)	10.4	10.4	10.4	10.4	10.4	10.2	10.6
PCO2(MEQ/L)	21.8	26.0	26.2	26.0	26.0	17.5	21.8
PH	7.363	7.348	7.350	7.395	7.395	7.354	7.355
PROTEIN(GZ)	6.80	6.30	6.20				7.10
PCO2(MMHG)	36.8	46.0	46.9		41.4	30.0	37.9

Serum Electrophoresis
(All Values = gm %)

Dog No.: 1074 Necropsy Date: 31 March 1976
 Dose Level (Mg/Day): 10 Day: 372

Sampling Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	<u>α-1</u>	<u>α-2</u>	<u>β-1</u>	<u>β-2</u>	<u>γ</u>
		Albumin	Globulin							
-3	-	-	-	-	-	-	-	-	-	-
0	6.3	-	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-	-
20	8.5	3.7	4.8	0.763	1.0	1.1	0.7	0.8	1.2	1.2
39	7.0	4.6	2.4	1.892	0.6	0.7	0.8	0.0	0.3	0.3
50	7.6	5.4	2.2	2.471	0.6	0.0	1.2	0.0	0.3	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Total</u> <u>Lipid Extract</u>
1.86	36 44

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1074F
DAY ONE DATE		032675
INITIAL BODY WEIGHT		7.3 Kg
FINAL BODY WEIGHT		

COMPOUND	HCB
DOSE	10 mg/dog/day
ROUTE	oral

[illegible]

Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1074F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>3/31/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>3:00 PM</u>
PATHOLOGY NUMBER	<u>76-2214</u>	DATE KILLED	<u>3/31/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>372</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the stomach at the junction of the body and pyloric antrum is a 2.0 x 0.5 cm strip of approximately 20 nodular bodies averaging 0.5 to 1.0 mm in diameter.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa of the pyloric antrum are a moderate number of small to medium sized lymphoid nodules.

ANIMAL ID: D01078
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/05	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	21-	0	29	84	142	264	348
--HEMATOLOGY--							
HCT(%)	43	49	38	49	45	49	44
HGB(GX)	15.8	17.1	14.1	15.6	16.8	17.0	16.3
RBC(10 ¹⁶ /CMH)	5.68	6.84	5.53	6.40	6.77	7.31	6.78
WBC(10 ¹³ /CMH)	7.14	9.29	8.83	7.95	8.61	6.54	11.48
NEUT,I(2WBC)	0.0	0.0	7.0	0.0	0.0	1.0	2.0
NEUT,M(2WBC)	51.0	37.0	33.0	37.0	47.0	53.0	54.0
NEUT,M(10 ¹³)	3.64	3.44	2.91	2.94	4.05	3.47	6.20
LYMPHO(2WBC)	42.0	53.0	45.0	50.0	38.0	41.0	39.0
LYMPHO(10 ¹³)	3.00	4.92	3.97	3.98	3.27	2.68	4.48
MONO(2WBC)	6.0	0.0	3.0	1.0	8.0	1.0	0.0
EOSINO(2WBC)	1.0	10.0	12.0	12.0	7.0	4.0	5.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(2RBC)	0.8	0.3	0.4	0.4	0.5	0.1	0.4
THR(10 ¹⁴ /CMH)	16	17	31	30	18	23	27
PROTIME(SEC)	9.4	8.9	6.4	10.0	8.5	6.4	6.9

--BLOOD CHEM--

BUN(MGX)	19.0	18.7	21.1	21.3	13.6	19.2	26.2
BS(MGX)	91	88	87	68	83	70	65
AP(KAU)	10.2	4.8	5.9	4.9	4.4	3.7	5.5
SGOT(RFU/ML)	18	16	11	11	7	13	12
SGPT(RFU/ML)	29	18	12	16	9	10	12
BILI(MGX)							
CL-(MEQ/L)	118	114	113	115	111	115	119
CA++(MGX)	9.8	10.2	10.4	10.2	11.0	10.6	10.6
PCO2(MEQ/L)	20.0	23.2	25.8	23.8	27.5	21.2	21.8
PH	7.322	7.354	7.350	7.340	7.382	7.334	7.289
PROTEIN(GX)	6.00	5.40	5.70	42.8	45.3	38.2	6.60
PCO2(MMHG)	37.0	40.8	45.3	42.8	45.3	38.2	43.7

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1078 Necropsy Date: 31 March 1976
Dose Level (Mg/Day): 10 Day: 372

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	9.8	3.4	6.4	0.541	1.9	1.2	1.1	1.5	0.7
0	5.4	2.4	3.0	0.780	1.0	0.5	0.7	0.4	0.3
13	-	-	-	-	-	-	-	-	-
20	7.8	3.3	4.5	0.717	1.1	1.2	0.6	0.9	0.7
39	6.6	4.1	2.5	1.590	0.8	0.5	0.4	0.5	0.3
50	7.4	5.2	2.2	2.368	0.6	0.6	0.8	0.0	0.2

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
29	36

Bile
1.54

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1078F
DAY ONE DATE		032675
INITIAL BODY WEIGHT		<u>9.4 Kg</u>
FINAL BODY WEIGHT		

COMPOUND	HCb
DOSE	10 mg/dog/day
ROUTE	oral

Treatment Date	A(AU/11-16)	D424750	62075081975	121575030876
Day in Study	I(AU/17-19)	29	86	146
Sp. Gr.	R(U1/20-24)	1.016	1.055	1.056
pH	R(U1/25-29)	8	7	8
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	0	trace	1+

Triple Phosphates	I(U2/20-24)	1+	2+	2+
Uric Acid	I(U2/25-29)			
Calcium Salts	I(U2/30-34)			
Other	A(U2/35-39)			
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	gran.	
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	0	0-1
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-2	*	1-2
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)	0-3	2-15	0-4
Mucous	I(U2/60-69)			
Appearance	I(U2/70-80)	pale	yellow	cl. y cl. y

Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1078F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>3/31/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>1:00 PM</u>
PATHOLOGY NUMBER	<u>76-2213</u>	DATE KILLED	<u>3/31/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>372</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the stomach at the region of the pyloric antrum are approximately 150 nodular bodies, each averaging 2 to 3 mm in diameter.

MICROSCOPIC OBSERVATIONS:

Stomach, pyloric antrum: Visible in the mucosa were a moderate number of medium sized lymphoid nodules.

ANIMAL ID: D01084
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/05	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	21-	0	29	84	142	264	348
---HEMATOLOGY---							
HCT(%)	44	47	43	45	43	48	43
HGB(GZ)	16.0	16.2	15.7	15.3	15.2	16.3	15.9
RBC(10 ¹⁶ /CMH)	5.94	6.46	6.04	6.03	6.16	6.55	6.59
WBC(10 ¹³ /CMH)	8.01	9.82	9.47	13.25	11.23	10.63	10.94
NEUT,I(ZWBC)	0.0	0.0	6.0	0.0	0.0	5.0	1.0
NEUT,M(ZWBC)	50.0	44.0	41.0	54.0	50.0	46.0	49.0
NEUT,H(10 ¹³)	4.01	4.32	3.88	7.16	5.62	4.89	5.36
LYMPHO(ZWBC)	45.0	44.0	46.0	41.0	31.0	35.0	40.0
LYMPHO(10 ¹³)	3.60	4.32	4.36	5.43	3.48	3.72	4.38
MONO(ZWBC)	2.0	2.0	1.0	1.0	3.0	2.0	0.0
EOSINO(ZWBC)	3.0	10.0	6.0	4.0	16.0	12.0	10.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.7	0.9	0.4	0.5	1.1	0.7	0.5
THR(10 ¹⁴ /CMH)	31	28	24	18	16	29	31
PROTIME(SEC)	7.9	10.5	7.9	11.4	8.4	6.9	7.4

---BLOOD CHEM---

BUN(MGZ)	18.1	20.1	16.4	21.7	16.4	16.8	32.3
BS(MGZ)	83	85	85	67	84	84	76
AP(KAU)	5.1	4.9	4.0	3.7	3.3	2.2	4.6
SGOT(RFU/ML)	17	18	9	11	11	17	14
SGPT(RFU/ML)	24	17	13	15	12	15	15
BILI(MGZ)							
CL-(MEQ/L)	116	111	111	112	112	114	112
CA++(MGZ)	9.6	10.2	10.2	10.4	10.8	10.8	10.8
PCO2(MEQ/L)	23.8	25.5	26.8	24.3	26.0	20.8	21.2
PH	7.334	7.311	7.343	7.336	7.326	7.308	7.278
PROTEIN(GZ)	7.80	5.90	5.90	44.5	48.4	40.0	6.90
PCO2(MMHG)	43.2	49.2	48.0	44.5	48.4	40.0	44.1

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1084 Necropsy Date: 1 April 1976
 Dose Level (Mg/Day): 10 Day: 373

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				γ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$
-3	6.5	2.5	4.0	0.623	1.1	0.7	0.9	0.8
0	5.9	2.8	3.1	0.921	0.8	0.6	0.7	0.6
13	-	-	-	-	-	-	-	-
20	6.6	3.0	3.6	0.852	0.6	0.9	0.6	0.6
39	6.5	3.8	2.7	1.437	0.8	0.5	1.2	0.0
50	7.4	4.9	2.5	1.941	0.7	0.6	0.4	0.6

- 196 -

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
13	15

Bile
1.70

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1084F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>4/1/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>3:00 PM</u>
PATHOLOGY NUMBER	<u>76-2236</u>	DATE KILLED	<u>4/1/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>373</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the stomach at the junction of the body and pyloric antrum is a 2 cm² area containing numerous 1-2 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous lymphoid nodules. Some are small, others are large with germinal centers.

ANIMAL ID: D01085
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/03	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	23-	0	29	84	142	264	348
--HEMATOLOGY--							
HCT(%)	43	46	43	49	46	48	45
HGB(GX)	15.9	16.5	15.7	17.6	16.6	17.8	17.2
RBC(10 ¹⁶ /CMH)	6.00	6.51	6.23	6.59	6.79	7.15	7.12
WBC(10 ¹³ /CMH)	11.60	10.66	9.94	13.38	10.70	9.00	9.49
NEUT,I(ZWBC)	0.0	0.0	3.0	1.0	0.0	1.0	0.0
NEUT,M(ZWBC)	65.0	60.0	54.0	50.0	61.0	58.0	60.0
NEUT,M(10 ¹³)	7.54	6.40	5.37	6.69	6.53	5.22	5.69
LYMPHO(ZWBC)	29.0	26.0	33.0	49.0	33.0	31.0	30.0
LYMPHO(10 ¹³)	3.36	2.77	3.28	6.56	3.53	2.79	2.85
MONO(ZWBC)	3.0	5.0	3.0	0.0	3.0	1.0	2.0
EOSINO(ZWBC)	3.0	9.0	7.0	0.0	3.0	9.0	8.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.2	1.7	1.8	0.5	1.4	0.7	0.8
THR(10 ¹⁴ /CMH)	30	18	19	29	15	23	44
PROTIME(SEC)	7.9	7.9	6.9	9.9	8.4	6.4	7.4

--BLOOD CHEM--

BUN(MGX)	22.5	17.1	20.5	23.3	21.2	28.1	25.4
BS(MGX)	102	94	90	80	83	87	80
AP(KAU)	5.2	4.1	4.6	4.3	2.1	2.1	2.8
SGOT(RFU/ML)	19	16	12	15	9	11	18
SGPT(RFU/ML)	24	17	14	18	12	13	18
BILI(MGX)							
CL-(MEQ/L)	115	114	112	113	111	117	117
CA++(MGX)	9.8	11.1	10.6	10.6	11.0	10.4	9.6
PCO2(MEQ/L)	20.8	26.0	25.6	24.2	25.5	21.2	22.0
PH	7.341	7.303	7.370	7.362	7.350	7.311	7.350
PROTEIN(GX)	6.50	6.00	6.00				6.70
PCO2(MMHG)	36.9	51.3	43.1	41.2	44.9	41.0	37.6

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1085 Necropsy Date: 1 April 1976
Dose Level (Mg/Day): 10 Day: 373

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	8.1	3.6	4.5	0.800	1.3	1.2	0.9	0.7	0.5
0	6.0	2.6	3.4	0.770	0.9	0.8	0.5	0.7	0.4
13	-	-	-	-	-	-	-	-	-
20	7.7	3.3	4.4	0.737	0.8	1.0	0.4	0.9	1.4
39	6.8	3.7	3.1	1.226	0.6	0.7	1.4	0.0	0.3
50	6.6	4.4	2.2	2.030	0.7	0.0	0.4	0.7	0.4

- 200 -

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
93	122

Bile
6.00

URINALYSIS

ANIMAL NUMBER (A/2-10) D1085M
 DAY ONE DATE 032675
 INITIAL BODY WEIGHT 10.5 Kg
 FINAL BODY WEIGHT

COMPOUND HCB
 DOSE 10 mg/dog/day
 ROUTE oral

Treatment Date	AIAU/11-16)	042475	062075	081975	121575	030876														
Day in Study	I(U1/17-19)	29	86	146	265	346														
Sp. Gr.	R(U1/20-24)	1.054	1.055	1.050	1.060	1.020														
pH	R(U1/25-29)	9	6	6	6.5	8.5														
Sugar	I(U1/30-34)	0	0	0	0	0														
Ketones	I(U1/35-39)	0	0	0	0	0														
Blood	I(U1/40-44)	0	0	0	0	0														
Protein	I(U1/45-49)	1+	1+	1+	1+	0														
MICROSCOPIC																				
Triple Phosphates	I(U2/20-24)	1+	4+	3+	3+	1+														
Uric Acid	I(U2/25-29)																			
Calcium Salts	I(U2/30-34)																			
Other	A(U2/35-39)					sperm														
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy																
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	*	0-5	2-3	0														
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-5	*	0	5-7	0-1														
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-6	*	6-10	3-4	2-3														
Mucous	I(U2/60-69)																			
Appearance	I(U2/70-90)	yellow	yellow	cl.y	dk cl.y	cl pl y														

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1085M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>4/1/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>9:00 AM</u>
PATHOLOGY NUMBER	<u>76-2235</u>	DATE KILLED	<u>4/1/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>373</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, fundus, body, lesser curvature: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa displays many small nodular bodies. These vary from 1-2 mm in diameter. The total number is about 300-400. The distribution is unusual in that the pyloric antrum shows none. Nearly all of the nodules are along the lesser curvature of the body and in the fundus, with a smaller number in the body adjoining the pyloric antrum. No other sections of the digestive tract show nodular bodies.

MICROSCOPIC OBSERVATIONS:

Stomach: Numerous medium sized lymphoid nodules are visible in the mucosa.

ANIMAL ID: D01097
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	22-	0	29	84	142	264	348
---HEMATOLOGY---							
HCT(%)	41	47	40	48	47	47	47
HGB(GZ)	15.1	16.1	15.0	16.5	16.5	16.8	18.4
RBC(10 ¹⁶ /CMH)	5.59	6.28	5.59	6.15	6.61	6.75	7.28
WBC(10 ¹³ /CMH)	10.89	11.74	11.60	11.33	10.36	8.00	10.47
NEUT,I(ZWBC)	0.0	0.0	3.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	71.0	45.0	54.0	62.0	64.0	69.0	77.0
LYMPHO(ZWBC)	7.73	5.28	6.26	7.02	6.63	5.52	8.06
LYMPHO(10 ¹³)	22.0	36.0	36.0	21.0	28.0	27.0	17.0
MONO(ZWBC)	2.40	4.23	4.18	2.38	2.90	2.16	1.78
EOSINO(ZWBC)	3.0	2.0	1.0	8.0	1.0	2.0	0.0
BASO(ZWBC)	4.0	17.0	6.0	9.0	7.0	2.0	6.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.2	0.5	0.7	0.5	0.8	0.4	0.9
THR(10 ¹⁴ /CMH)	36	19	18	24	20	26	39
PROTIME(SEC)	6.9	7.9	6.4	8.9	8.9	6.9	7.5

---BLOOD CHEM---

BUN(MGZ)	16.8	17.5	16.5	19.6	14.4	17.7	19.4
BS(MGZ)	77	95	85	71	100	83	82
AP(KAU)	3.9	3.5	4.7	4.7	2.1	1.9	1.6
SGOT(RFU/ML)	15	15	11	13	7	10	13
SGPT(RFU/ML)	15	14	12	15	12	16	18
BILI(MGZ)							
CL-(MEQ/L)	119	111	111	110	112	115	118
CA++(MGZ)	9.6	10.4	10.4	10.0	10.6	10.8	10.6
PCO2(MEQ/L)	26.0	27.5	25.8	24.0	26.8	22.0	20.8
PH	7.384	7.326	7.338	7.319	7.359	7.330	7.315
PROTEIN(GZ)	6.70	5.90	6.30	45.6	46.3	40.2	7.00
PCO2(MMHG)	42.1	51.5	46.5	45.6	46.3	40.2	39.6

Serum Electrophoresis
(All Values = gm %)

Dog No.: 1097 Necropsy Date: 2 April 1976
 Dose Level (Mg/Day): 10 Day: 374

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Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α-1		α-2		β-1		β-2		γ
	Protein	Albumin	Globulin										
-3	8.3	3.3	5.0	0.641	0.4		1.2		1.0		0.7		0.5
0	5.9	2.5	3.4	0.759	0.9		0.9		0.7		0.7		0.2
13	-	-	-	-	-		-		-		-		-
20	8.0	3.3	4.7	0.714	1.0		1.3		0.6		0.9		0.9
39	7.0	4.1	2.9	1.455	1.2		0.0		1.0		0.0		0.6
50	7.5	5.3	2.2	2.385	0.2		0.6		0.4		0.8		0.2

- 204 -

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
22	28

Bile
2.25

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1097M
DAY ONE DATE		032675
INITIAL BODY WEIGHT		9.7 Kg
FINAL BODY WEIGHT		

COMPOUND	HCB
DOSE	10 mg/dog/day
ROUTE	oral

Treatment Date	A(U)/11-16)	042475	5061975	581975	121575	030876																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																									</
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★ **Too numerous to count**

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1097M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>4/2/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>11:00 AM</u>
PATHOLOGY NUMBER	<u>76-2238</u>	DATE KILLED	<u>4/2/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>374</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01103
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/26	4/24	6/18	8/15	12/15	3/08
DAY:	20-	0	29	84	142	264	348
---HEMATOLOGY---							
HCT(X)	41	42	43	48	46	44	50
HGB(GZ)	15.0	14.8	14.7	16.7	15.2	17.1	18.2
RBC(10 ⁶ /CMH)	5.40	5.59	5.66	7.00	6.27	6.50	7.05
WBC(10 ³ /CMH)	9.53	7.92	7.59	10.04	6.50	7.41	9.09
NEUT,I(XWBC)	0.0	0.0	3.0	0.0	0.0	4.0	0.0
NEUT,M(XWBC)	65.0	52.0	36.0	43.0	47.0	66.0	69.0
NEUT,H(10 ³)	6.19	4.12	2.73	4.32	3.06	4.89	6.27
LYMPHO(XWBC)	30.0	34.0	55.0	47.0	37.0	20.0	18.0
LYMPHO(10 ³)	2.86	2.69	4.17	4.72	2.41	1.48	1.64
MONO(XWBC)	3.0	1.0	0.0	1.0	0.0	4.0	5.0
EOSINO(XWBC)	2.0	13.0	6.0	9.0	16.0	6.0	8.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	0.3	0.6	0.5	0.9	0.5	0.1	1.0
THR(10 ⁴ /CMH)	26	20	16	21	13	21	41
PROTIME(SEC)	6.9	9.1	6.9	9.5	8.9	7.4	7.4

---BLOOD CHEM---

BUN(MGZ)	14.6	15.1	15.0	20.2	9.3	17.5	20.9
BS(MGZ)	84	100	91	77	98	87	86
AP(KAU)	3.3	2.7	4.3	3.0	2.5	1.6	1.8
SGOT(RFU/ML)	66	16	11	13	10	14	15
SGPT(RFU/ML)	43	14	13	12	6	13	13
BILI(MGZ)							
CL-(MEQ/L)	111	114	114	111	109	116	120
CA++(MGZ)	10.0	11.0	9.8	9.8	10.2	10.6	10.4
PCO2(MEQ/L)	23.8	25.5	25.8	22.6	26.2	22.5	22.0
PH	7.312	7.389	7.396	7.298	7.372	7.372	7.375
PROTEIN(GZ)	13.20	5.70	5.80				6.50
PCO2(MMHG)	45.7	41.1	40.9	44.4	44.1	37.5	36.2

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1103 Necropsy Date: 30 March 1976
 Dose Level (Mg/Day): 10 Day: 371

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.3	2.5	3.8	0.667	0.8	0.9	0.5	0.8	0.8
0	5.7	2.8	2.9	0.983	0.8	0.7	0.9	0.3	0.3
13	-	-	-	-	-	-	-	-	-
20	6.7	2.6	4.1	0.631	0.8	1.0	1.0	0.4	0.9
39	6.2	3.7	2.5	1.509	0.5	0.6	0.4	0.8	0.3
50	6.7	4.8	1.9	2.458	0.6	0.0	1.1	0.0	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
32	39

Bile
2.31

URINALYSIS

ANIMAL NUMBER. . . . (A/3-10) D1103M

DAY ONE DATE 032675

[illegible]

FINAL BODY WEIGHT

COMPOUND	HCB
1	1
2	2
3	3
4	4
5	5
6	6
7	7
8	8
9	9
10	10
11	11
12	12
13	13
14	14
15	15
16	16
17	17
18	18
19	19
20	20
21	21
22	22
23	23
24	24
25	25
26	26
27	27
28	28
29	29
30	30
31	31
32	32
33	33
34	34
35	35
36	36
37	37
38	38
39	39
40	40
41	41
42	42
43	43
44	44
45	45
46	46
47	47
48	48
49	49
50	50
51	51
52	52
53	53
54	54
55	55
56	56
57	57
58	58
59	59
60	60
61	61
62	62
63	63
64	64
65	65
66	66
67	67
68	68
69	69
70	70
71	71
72	72
73	73
74	74
75	75
76	76
77	77
78	78
79	79
80	80
81	81
82	82
83	83
84	84
85	85
86	86
87	87
88	88
89	89
90	90
91	91
92	92
93	93
94	94
95	95
96	96
97	97
98	98
99	99
100	100

DOSE	10 mg/day
...	...

ROUTE oral

Treatment Date	AIAU(11-16)	042475	062075	081975	121575	030876
Day in Study	I(AU/17-19)	29	86	146	265	346
Sp. Gr.	R(U1/20-24)	1.050	1.045	1.040	1.008	1.062
pH	R(U1/26-29)	9	6	6	7	6.5
Sugar	I(U1/30-34)	0	0	0	0	0
Ketones	I(U1/35-39)	0	0	0	0	0
Blood	I(U1/40-44)	0	0	0	0	0
Protein	I(U1/45-49)	1+	1+	trace	0	1+

		MICROSCOPIC	
Triple Phosphates	I(U2/20-24)	3+	3+
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)		
Other	A(U2/35-39)		sperm
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	fatty	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	*
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-1	* 0-1
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-3	10-15 0-2
Mucous	I(U2/60-69)		
Appearance	I(U2/70-80)	yellow	yellow cldky

Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1103M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>3/30/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>3:00 PM</u>
PATHOLOGY NUMBER	<u>76-2159</u>	DATE KILLED	<u>3/30/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>371</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the mucosa of the stomach at the junction of the body and pyloric antrum there is a 1" strip of nodules.

MICROSCOPIC OBSERVATIONS:

Stomach: Visible in the mucosa at the junction of the body and pyloric antrum are a small number of small and medium sized lymphoid nodules.

ANIMAL ID: D01120
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/26/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 1.000000
 (MG/DOG): 10.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/17 3/26 4/24 6/18 8/15 12/15 3/08
 DAY: 9- 0 29 84 142 264 348

---HEMATOLOGY---

HCT(%)	45	42	46	46	46	43	49
HGB(GZ)	16.5	15.5	15.6	14.8	16.5	16.4	18.8
RBC(10 ¹⁶ /CMH)	6.42	5.99	6.01	5.93	6.61	6.45	7.40
WBC(10 ¹³ /CMH)	8.87	8.90	9.37	12.06	10.15	12.80	14.22
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	0.0	1.0	1.0
NEUT,M(ZWBC)	33.0	42.0	35.0	47.0	55.0	63.0	56.0
NEUT,M(10 ¹³)	2.93	3.74	3.28	5.67	5.58	8.06	7.96
LYMPHO(ZWBC)	58.0	51.0	50.0	49.0	45.0	33.0	36.0
LYMPHO(10 ¹³)	5.14	4.54	4.69	5.91	4.57	4.22	5.12
MONO(ZWBC)	1.0	3.0	8.0	0.0	0.0	0.0	1.0
EOSINO(ZWBC)	8.0	4.0	7.0	4.0	0.0	3.0	6.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.1	0.2	0.1	0.1	0.3	0.3	0.4
THR(10 ¹⁴ /CMH)	27	32	33	21	17	27	42
PROTIME(SEC)	6.4	7.9	6.5	9.9	8.4	6.9	7.9

---BLOOD CHEM---

BUN(MGZ)	12.0	15.4	12.6	21.4	12.0	17.1	17.9
BS(MGZ)	101	87	78	83	93	78	74
AP(KAU)	8.0	5.6	5.9	3.7	2.4	2.1	1.5
SGOT(RFU/ML)	19	19	11	14	13	13	13
SGPT(RFU/ML)	16	16	14	14	9	12	12
BILI(MGZ)							
CL-(MEQ/L)	116	113	115	115	108	117	120
CA++(MGZ)	11.1	10.7	10.2	10.2	10.0	10.8	10.2
PCO2(MEQ/L)	21.0	26.5	25.8	26.0	26.8	21.5	23.5
PH	7.212	7.325	7.338	7.320	7.369	7.317	7.350
PROTEIN(GZ)	6.20	5.40	6.20	49.1	45.2	40.8	41.3
PCO2(MMHG)	50.8	49.8	46.4				

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1120

Dose Level (Mg/Day): 10

Necropsy Date: 1 April 1976

Day: 373

Sampling Time (Weeks)	Total		Albumin/Globulin (Ratio)					
	Protein	Albumin	Globulin	α -1	α -2	β -1	β -2	γ
-3	-	-	-	-	-	-	-	-
0	5.4	2.2	3.2	0.9	0.6	0.5	0.8	0.5
13	-	-	-	-	-	-	-	-
20	6.9	2.2	4.7	0.5	1.4	0.5	0.7	1.7
39	6.5	4.6	1.9	0.5	0.2	0.5	0.7	0.2
50	6.5	4.1	2.4	0.5	0.5	0.6	0.4	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
272	337

Bile
12.86

URINALYSIS

ANIMAL NUMBER (A/2-10) D1120F

DAY ONE DATE 032675

INITIAL BODY WEIGHT 6.7 Kg

FINAL BODY WEIGHT

COMPOUND HCB

DOSE 10 mg/dog/day

ROUTE oral

Treatment Date	A (A/11-16)	042475	062075	5081975	121575	030876
Day in Study	I (A/17-19)	29	86	146	265	346
Sp. Gr.	R (U1/20-24)	1.080	1.065	1.045	1.061	1.074
pH	R (U1/25-29)	8	6	6	6.5	6.5
Sugar	I (U1/30-34)	0	0	0	0	0
Ketones	I (U1/35-39)	0	0	0	0	0
Blood	I (U1/40-44)	0	0	0	0	0
Protein	I (U1/45-49)	trace	trace	trace	1+	1+
REAGENT STRIP						
Triple Phosphates	I (U2/20-24)	1+			1+	
Uric Acid	I (U2/25-29)					
Calcium Salts	I (U2/30-34)				1+	
Other	A (U2/35-39)					few dmcp
Casts/LPF 100X (Avg/Field)	I (U2/40-44)	0	0	waxy		
RBC/HPF 400X (Avg/Field)	I (U2/45-49)	0	0	0-5	0	1-2
WBC/HPF 400X (Avg/Field)	I (U2/50-54)	2-8	10-15	0-4	5-7	2-3
EPITH/HPF 400X (Avg/Field)	I (U2/55-59)	1-7	0-1	0-3	3-4	2-3
Mucous	I (U2/60-69)					
Appearance	I (U2/70-80)	yellow	yellow	yellow	dk cl y	cl dky
MICROSCOPIC						

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1120F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>032675</u>	NECROPSY DATE	<u>4/1/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>10</u>	HOUR DIED	<u>11:00 AM</u>
PATHOLOGY NUMBER	<u>76-2234</u>	DATE KILLED	<u>4/1/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Good</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>373</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa shows numerous nodules especially in the pyloric antrum where it joins the body. Two nodules about 3 mm in diameter are on the esophageal mucosa about 1 cm from the cardia.

MICROSCOPIC OBSERVATIONS:

Stomach, pyloric antrum: Visible in the mucosa are numerous large and small lymphoid nodules.

ANIMAL ID: D01105
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/06 3/27 4/25 6/19 8/18
 DAY: 22- 1- 28 83 143

--HEMATOLOGY--

HCT(Z)	41	43	45	50	40
HGB(GZ)	14.9	14.9	16.8	16.5	16.2
RBC(10 ¹⁶ /CMH)	5.63	6.18	6.41	6.78	6.33
WBC(10 ¹³ /CMH)	9.77	11.66	8.52	8.40	13.8
NEUT,I(ZWBC)	0.0	0.0	1.0	0.0	0.0
NEUT,M(ZWBC)	50.0	62.0	46.0	49.0	67.0
NEUT,H(10 ¹³)	4.89	7.23	3.92	4.12	9.30
LYMPHO(ZWBC)	40.0	32.0	46.0	46.0	21.0
LYMPHO(10 ¹³)	3.91	3.73	3.92	3.86	2.90
MONO(ZWBC)	4.0	3.0	1.0	1.0	4.0
EOSINO(ZWBC)	6.0	3.0	6.0	4.0	8.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.4	0.6	0.4	1.3	0.5
THR(10 ¹⁴ /CMH)	28	27	17	22	25
PROTIME(SEC)	6.9	8.9	7.3	6.4	8.4

--BLOOD CHEM--

BUN(MGZ)	20.8	13.7	12.6	15.6	19.2
BS(MGZ)	69	74	73	77	72
AP(KAU)	4.5	4.9	5.1	3.1	2.8
SGOT(RFU/ML)	15	12	11	16	14
SGPT(RFU/ML)	24	15	13	15	13
BILI(MGZ)					
CL-(MEQ/L)	113	116	115	113	111
CA++(MGZ)	10.4	10.2	10.2	10.6	9.6
PCO2(MEQ/L)	22.2	23.8	22.8	20.8	21.8
PH	7.304	7.333	7.369	7.375	7.322
PROTEIN(GZ)	6.30	6.10			
PCO2(MMHG)	43.2	43.8	38.1	34.1	40.8

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1105

Dose Level (Mg/Day): 1

Necropsy Date: 21 August 1975

Day: 148

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.5	2.3	4.2	0.557	1.1	0.9	0.5	0.7	0.9
0	6.1	3.5	2.6	1.326	0.7	0.5	0.5	0.5	0.5
13	-	-	-	-	-	-	-	-	-
20	7.4	3.2	4.2	0.743	0.7	1.4	0.4	1.0	0.8
39									
50									

Sacrificed

Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	0.29	
	8.8	13.3

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1105M
DAY ONE DATE		032775
INITIAL BODY WEIGHT		10.9 Kg
FINAL BODY WEIGHT		9.7 Kg

COMPOUND		HCB
DOSE		1 mg/dog/day
ROUTE		oral

Treatment Date	AIAU(11-16)	042675	062375	082175
Day in Study	I(AU/17-19)	30	88	147
Sp. Gr.	R(U1/20-24)	1.075	1.040	1.055
pH	R(U1/25-29)	6	9	6
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	1+	1+	1+

MICROSCOPIC				
Triple Phosphates	I(U2/20-24)	1+		
Uric Acid	I(U2/25-29)		2+	
Calcium Salts	I(U2/30-34)			
Other	A(U2/35-39)			
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0	5-10
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	2-5	0-1	*
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)	0	0-3	5-10
Mucous	I(U2/60-69)			
Appearance	I(U2/70-80)	brown	dk.y	yellow

Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1105M</u>	NECROPSY DATE	<u>8/21/75</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>2:30 PM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>8/21/75</u>
PATHOLOGY NUMBER	<u>75-6100</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>148</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa in a 6 x 2 cm area at the junction of the body and pyloric antrum is covered with 2-4 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous lymphoid nodules.

ANIMAL ID: D01124
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT : 938872
 DAILY DOSE
 (MG/KG) :
 (MG/DOG):
 SCHEDULE : DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/27 4/25 6/19 8/18
 DAY: 9- 0 29 84 144

--HEMATOLOGY--

	47	46	45	45	45
HCT(%)	47	46	45	45	45
HGB(GZ)	16.5	17.1	17.2	16.2	16.4
RBC(10 ¹⁶ /CMH)	6.65	6.68	6.58	6.59	6.36
WBC(10 ¹³ /CMH)	8.67	9.17	8.79	7.45	8.20
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	57.0	57.0	59.0	55.0	69.0
NEUT,L(10 ¹³)	4.94	5.23	5.19	4.10	5.66
LYMPHO(ZWBC)	38.0	36.0	26.0	38.0	21.0
LYMPHO(10 ¹³)	3.29	3.30	2.29	2.83	1.72
MONO(ZWBC)	2.0	1.0	6.0	3.0	4.0
EOSINO(ZWBC)	3.0	6.0	9.0	4.0	6.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.7	0.2	0.6	0.4	1.6
THR(10 ¹⁴ /CMH)	24	33	21	22	16
PROTIME(SEC)	7.9	6.9	5.9	5.9	7.0

--BLOOD CHEM--

	21.1	17.1	12.6	20.0	15.2
BUN(MGZ)	21.1	17.1	12.6	20.0	15.2
BS(MGZ)	88	83	78	82	88
AP(KAU)	3.5	4.1	4.3	3.0	2.5
SGOT(RFU/ML)	15	15	13	13	11
SGPT(RFU/ML)	21	25	24	16	16
BILI(MGZ)					
CL-(MEQ/L)	117	112	116	117	113
CA++(MGZ)	10.2	10.6	10.6	10.2	10.6
PCO2(MEQ/L)	22.8	24.2	24.0	24.8	22.2
PH	7.292	7.354	7.390	7.390	7.374
PROTEIN(GZ)	6.10	6.30			
PCO2(MMHG)	45.7	42.7	38.4	39.8	37.0

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1124 Necropsy Date: 21 August 1975
 Dose Level (Mg/Day): 1 Day: 148

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.3	3.0	3.3	0.935	0.8	0.6	0.8	0.6	0.4
13	-	-	-	-	-	-	-	-	-
20	7.4	3.1	4.3	0.740	0.7	1.3	1.4	-	0.9
39									
50									

Sacrificed

- 220 -

Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	0.21	
	4.5	12.5

URINALYSIS

ANIMAL NUMBER (A/3-10) D1124F
 DAY ONE DATE 032775
 INITIAL BODY WEIGHT 6.6 Kg
 FINAL BODY WEIGHT 6.47 Kg

COMPOUND HCB
 DOSE 1 mg/dog/day
 ROUTE oral

Treatment Date	AIAU/11-16	042875	062375	082175
Day in Study	I(AU/17-19)	32	88	147
Sp. Gr.	R(U1/20-24)	1.060	1.037	1.040
pH	R(U1/25-29)	6	9	8
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	trace	1+	0

MICROSCOPIC																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																												</
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NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1124F</u>	NECROPSY DATE	<u>8/21/75</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:30 AM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>8/21/75</u>
PATHOLOGY NUMBER	<u>75-6101</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>148</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the gastric mucosa of the pyloric antrum are a moderate number of 3-4 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous lymphoid nodules.

ANIMAL ID: D01119
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):
 0.100000
 1.00000

NO GRADES

DATE: 3/17 3/27 4/25 6/19 8/18
 DAY: 10- 0 29 84 144

--HEMATOLOGY--

HCT(%)	47	43	43	41	45
HGB(GZ)	16.4	16.1	15.3	13.7	15.7
RBC(10 ¹⁶ /CMH)	6.42	6.07	5.94	5.54	5.96
WBC(10 ¹³ /CMH)	8.89	7.49	5.48	5.46	7.95
NEUT,I(%WBC)	2.0	0.0	0.0	0.0	0.0
NEUT,M(%WBC)	49.0	53.0	30.0	32.0	48.0
NEUT,H(10 ¹³)	4.36	3.97	1.64	1.75	3.82
LYMPHO(%WBC)	39.0	40.0	61.0	52.0	38.0
LYMPHO(10 ¹³)	3.47	3.00	3.34	2.84	3.02
MONO(%WBC)	4.0	3.0	2.0	2.0	8.0
EOSINO(%WBC)	6.0	4.0	7.0	14.0	6.0
BASO(%WBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(%WBC)	0.0	0.0	0.0	0.0	0.0
RET(%RBC)	0.1	0.1	0.2	0.4	0.9
THR(10 ¹⁴ /CMH)	52	28	25	23	18
PROTIME(SEC)	6.5	7.4	6.4	7.4	7.9

--BLOOD CHEM--

BUN(MGZ)	11.4	12.7	11.8	12.1	14.8
BS(MGZ)	111	84	86	90	75
AP(KAU)	7.8	6.5	6.3	4.2	3.3
SGOT(RFU/ML)	17	15	15	15	13
SGPT(RFU/ML)	18	18	15	15	15
BILI(MGZ)					
CL-(MEQ/L)	117	112	112	116	112
CA++(MGZ)	11.3	10.4	10.0	9.8	9.8
PCO2(MEQ/L)	23.8	25.8	22.8	23.2	23.8
PH	7.278	7.368	7.400	7.411	7.349
PROTEIN(GZ)	6.40	6.20			
PCO2(MMHG)	49.2	43.6	35.7	35.3	42.0

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1119

Dose Level (Mg/Day): 1

Necropsy Date: 22 August 1975

Day: 149

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.2	2.7	3.5	0.795	0.9	0.8	0.7	0.7	0.4
13	-	-	-	-	-	-	-	-	-
20	7.8	3.1	4.7	0.654	0.7	1.1	1.1	0.9	0.9
39									
50									

Sacrificed

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
7.3	9.7

Bile
0.18

URINALYSIS

ANIMAL NUMBER: (A/3-10) — D1119M

COMPOUND HCB

DAY ONE DATE 032775

DOSE . . . 1 mg/day

INITIAL BODY WEIGHT. 9.5 Kg

1

FINAL BODY WEIGHT

ROUTE **ααα**

Treatment Date	A(U)/11-16)	O42875062075082175
Day in Study	I(AU/17-19)	32 85 147
Sp. Gr.	R(U)/20-24)	1.028 1.080 1.050
pH	R(U)/25-29)	6 6 6
Sugar	I(U)/30-34)	0 0 0
Ketones	I(U)/35-39)	0 0 0
Blood	I(U)/40-44)	0 0 0
Protein	I(U)/45-49)	0 trace trace

MICROSCOPIC	I(U2/20-24)	2+	1+
Triple Phosphates			
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)		
Other	A(U2/35-39)	bact.	
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0 grain.	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	2 0 0	*
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-10 5-10 0-3	
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)	0-2 5-10 0-3	
Mucous	I(U2/60-69)		
Appearance	I(U2/70-80)	yellow yb yellow	

*** Too numerous to count**

ANIMAL ID: D01126
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):
 0.100000
 1.00000

NO GRADES

DATE: 3/18 3/27 4/25 6/19 8/18
 DAY: 9- 0 29 84 144

--HEMATOLOGY--

HCT(%)	50	42	48	47	47
HGB(GZ)	17.3	15.4	17.2	16.6	16.1
RBC(10 ¹⁶ /CMM)	7.10	6.22	6.67	7.02	6.58
WBC(10 ¹³ /CMM)	10.06	8.86	6.90	8.15	10.31
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	51.0	48.0	36.0	35.0	47.0
NEUT,L(10 ¹³)	5.13	4.25	2.48	2.85	4.85
LYMPHO(ZWBC)	38.0	45.0	49.0	55.0	48.0
LYMPHO(10 ¹³)	3.82	3.99	3.38	4.48	4.95
MONO(ZWBC)	3.0	2.0	6.0	4.0	0.0
EOSINO(ZWBC)	8.0	5.0	9.0	6.0	5.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORML(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.4	0.3	0.8	0.5	0.5
THR(10 ¹⁴ /CMM)	21	37	18	12	17
PROTIME(SEC)	8.4	9.4	6.4	5.9	7.4

--BLOOD CHEM--

BUN(MGZ)	16.1	21.4	16.7	18.1	14.2
BS(MGZ)	84	83	74	82	89
AP(KAU)	3.6	4.2	4.4	3.7	3.7
SGOT(RFU/ML)	17	15	18	15	12
SGPT(RFU/ML)	18	13	22	12	12
BILI(MGZ)					
CL-(MEQ/L)	114	117	116	115	112
CA++(MGZ)	10.8	10.8	11.0	10.4	9.8
PCO2(MEQ/L)	24.8	25.8	24.0	24.0	24.0
PH	7.293	7.346	7.380	7.367	7.331
PROTEIN(GZ)	7.50	6.30			
PCO2(MMHG)	49.6	45.6	39.7	40.6	44.6

Serum Electrophoresis
(All Values = gm %)

Dog No.: 1126 Necropsy Date: 22 August 1975
 Dose Level (Mg/Day): 1 Day: 149

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.3	2.9	3.4	0.859	1.0	0.7	0.6	0.8	0.3
13	-	-	-	-	-	-	-	-	-
20	8.7	3.3	5.4	0.609	1.0	1.6	1.0	1.0	0.8
39									
50				Sacrificed					

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Total Lipid Extract</u>
0.08	7.0
	8.6

URINALYSIS

ANIMAL NUMBER (A/3-10) D1126E
 DAY ONE DATE 032775
 INITIAL BODY WEIGHT 8.2 Kg
 FINAL BODY WEIGHT
 COMPOUND HCB
 DOSE 1 mg/dog/day
 ROUTE oral

Treatment Date	AIAU/11-16	042875	062375	082175
Day in Study	I(AU/17-19)	32	88	147
Sp. Gr.	R(U1/20-24)	1.062	1.034	1.045
pH	R(U1/25-29)	6	8	6
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	trace	0	trace
REAGENT STRIP				
MICROSCOPIC				
Triple Phosphates	I(U2/20-24)		2+	
Uric Acid	I(U2/25-29)			
Calcium Salts	I(U2/30-34)			
Other	A(U2/35-39)			
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	0	0-5
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-2	5-10	*
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-2	0-2	0-6
Mucous	I(U2/60-69)			
Appearance	I(U2/70-90)	yellow	yellow	yellow

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1119M</u>	NECROPSY DATE	<u>8/22/75</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>1:30 PM</u>
DOSE Mg/Da:	<u>1</u>	DATE DIED	<u>8/22/75</u>
PATHOLOGY NUMBER	<u>75-6155</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>14 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>149</u>

SUMMARY:

DRUG INDUCED LESIONS

None.

ANIMAL NUMBER	<u>D1126F</u>	NECROPSY DATE	<u>8/22/75</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>3:00 PM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>8/22/75</u>
PATHOLOGY NUMBER	<u>75-6156</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>14 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>149</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01090
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.10000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/27 4/25 6/19 8/18 12/16 3/05
 DAY: 23- 0 29 84 144 264 344

--HEMATOLOGY--

HCT(Z)	49	46	47	40	45	52	48
HGB(GZ)	17.6	16.6	17.9	13.5	16.7	16.0	18.2
RBC(10 ⁶ /CMH)	6.32	6.26	6.39	5.61	6.29	6.78	7.19
WBC(10 ³ /CMH)	11.71	10.21	10.83	8.73	10.55	10.10	7.64
NEUT,I(ZWBC)	0.0	0.0	8.0	1.0	0.0	2.0	3.0
NEUT,M(ZWBC)	73.0	47.0	49.0	60.0	67.0	61.0	50.0
NEUT,H(10 ³)	8.55	4.80	5.31	5.24	7.07	6.16	3.82
LYMPHO(ZWBC)	23.0	41.0	31.0	22.0	21.0	23.0	36.0
LYMPHO(10 ³)	2.69	4.19	3.36	1.92	2.22	2.32	2.75
MONO(ZWBC)	3.0	3.0	3.0	6.0	3.0	8.0	3.0
EOSINO(ZWBC)	1.0	9.0	8.0	11.0	9.0	6.0	8.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.2	0.4	0.9	0.7	0.9	0.6	0.4
THR(10 ⁴ /CMH)	36	29	18	20	16	19	25
PROTIME(SEC)	6.5	10.4	7.5	7.9	7.4	6.9	8.9

--BLOOD CHEM--

BUN(MGZ)	16.8	16.1	15.0	16.4	18.6	22.3	14.4
BS(MGZ)	81	83	66	76	79	75	69
AP(KAU)	4.6	4.7	4.6	3.3	2.1	3.9	1.5
SGOT(RFU/ML)	19	15	12	10	14	15	15
SGPT(RFU/ML)	18	14	14	12	13	17	14
BILI(MGZ)							
CL-(MEQ/L)	120	116	116	115	109	117	115
CA++(MGZ)	10.4	9.8	10.6	10.0	10.2	10.4	10.4
PCO2(MEQ/L)	21.8	23.2	25.5	24.8	22.5	21.2	18.5
PH	7.235	7.302	7.284	7.296	7.270	7.315	7.308
PROTEIN(GZ)		5.80					6.30
PCO2(MMHG)	49.3	45.6	52.1	49.6	47.2	40.6	35.5

Serum Electrophoresis
(All Values = gm %)

Dog No.: 1090 Necropsy Date: 24 March 1976
 Dose Level (Mg/Day): 1 Day: 364

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				χ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	
-3	8.2	3.3	4.9	0.660	1.2	1.2	1.2	0.4
0	5.8	2.4	3.4	0.704	0.9	0.6	0.9	0.3
13	6.1	4.4	1.7	2.688	0.4	0.3	0.8	0.1
20	7.0	2.7	4.3	0.618	0.7	1.1	0.8	1.0
39	6.5	3.7	2.8	1.357	1.1	0.0	1.2	0.4
50	6.4	4.4	2.0	2.188	0.4	0.4	1.0	0.2

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<u>Tissue HCB (PPM) Level at Necropsy</u>		
Bile	Fat	
	Total	Lipid Extract
0.446	3.19	3.99

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1090F
DAY ONE DATE		032775
INITIAL BODY WEIGHT		7.6 Kg
FINAL BODY WEIGHT		

COMPOUND	HCB
DOSE	1 mg/dog/day
ROUTE	oral
1	
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Treatment Date	A(U/11-16)	042675	062775	082175	121775	030576
Day in Study	I(U/17-19)	30	92	147	266	345
Sp. Gr.	R(U/20-24)	1.075	1.040	1.045	1.060	1.052
pH	R(U/25-29)	6	8	7	6.5	6.5
Sugar	I(U/30-34)	0	0	0	0	0
Ketones	I(U/35-39)	0	0	0	0	0
Blood	I(U/40-44)	0	0	0	0	0
Protein	I(U/45-49)	1	1+	trace	0	2+

		MICROSCOPIC	
Triple Phosphates	I(U/20-24)	1+	3+
Uric Acid	I(U/25-29)		
Calcium Salts	I(U/30-34)	1+	2+
Other	A(U/35-39)		
Casts/LPF 100X (Avg/Field)	I(U/40-44)	0	0
RBC/HPF 400X (Avg/Field)	I(U/45-49)	0	0
WBC/HPF 400X (Avg/Field)	I(U/50-54)	0-3	0-1
EPI TH/HPF 400X (Avg/Field)	I(U/55-59)	mod.	5-10
Mucous	I(U/60-69)		0-6
Appearance	I(U/70-80)	yellow	low cl dky

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1090F</u>	NECROPSY DATE	<u>3/24/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HC8</u>	HOUR DIED	<u>2:45 PM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/24/76</u>
PATHOLOGY NUMBER	<u>76-2082</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>368</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01092
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	23-	0	29	84	144	264	344
--HEMATOLOGY--							
HCT(Z)	45	43	42	51	47	61	49
HGB(GZ)	16.5	15.9	14.7	17.1	19.2	20.3	18.4
RBC(10 ¹⁶ /CMH)	6.22	6.07	5.60	7.18	7.24	8.46	7.74
WBC(10 ¹³ /CMH)	8.39	7.75	7.55	7.92	9.83	7.40	7.79
NEUT,I(ZWBC)	0.0	0.0	7.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	74.0	50.0	44.0	47.0	65.0	52.0	63.0
NEUT,M(10 ¹³)	6.21	3.88	3.32	3.72	6.39	3.85	4.91
LYMPHO(ZWBC)	26.0	44.0	42.0	48.0	30.0	35.0	25.0
LYMPHO(10 ¹³)	2.18	3.41	3.17	3.80	2.95	2.59	1.95
MONO(ZWBC)	0.0	2.0	3.0	0.0	2.0	5.0	1.0
EOSINO(ZWBC)	0.0	4.0	4.0	5.0	3.0	8.0	11.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.1	0.1	0.6	0.5	0.8	1.2	1.2
THR(10 ¹⁴ /CMH)	32	35	50	25	20	30	41
PROTIME(SEC)	6.4	7.9	6.9	7.4	8.4	7.4	8.4

--BLOOD CHEM--

BUN(MGZ)	16.8	20.4	19.4	20.1	22.0	22.9	20.9
BS(MGZ)	77	72	76	73	64	79	57
AP(KAU)	3.9	4.8	5.3	3.6	4.1	2.4	4.3
SGOT(RFU/ML)	13	13	15	18	13	15	15
SGPT(RFU/ML)	15	13	15	13	12	15	13
BILI(MGZ)							
CL-(MEQ/L)	116	110	111	110	109	120	113
CA++(MGZ)	10.6	11.0	10.0	10.4	10.6	10.6	10.4
PCO2(MEQ/L)	25.3	26.8	26.2	24.8	20.8	17.0	26.3
PH	7.338	7.360	7.347	7.403	7.364	7.364	7.336
PROTEIN(GZ)	6.70	6.10					6.10
PCO2(MMHG)	46.0	46.6	47.0	38.6	34.9	28.0	48.5

Serum Electrophoresis
(All Values = gm %)

Dog No.: 1092

Dose Level (Mg/Day): 1

Necropsy Date: 23 March 1976

Day: 363

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	7.8	3.7	4.1	0.892	1.4	0.9	1.2	0.3	0.4
0	6.1	2.5	3.6	0.710	1.3	0.8	0.9	0.4	0.2
13	6.6	4.8	1.8	2.609	0.3	0.4	0.9	0.0	0.2
20	7.8	3.3	4.5	0.735	0.9	1.2	1.0	0.6	0.9
39	7.0	4.2	2.8	1.474	0.9	0.5	0.8	0.1	0.4
50	6.5	4.8	1.7	2.719	0.6	0.0	0.8	0.0	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
6.38	9.65

Bile
0.303

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1092F</u>	NECROPSY DATE	<u>3/24/76</u>
DAY ONE DATE	<u>3/27/71</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>3:30 PM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/23/76</u>
PATHOLOGY NUMBER	<u>76-2031</u>	PRENECROPSY CONDITION	<u>Good</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>368</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa in the area of the pyloric antrum is covered by a moderate number of 1-3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous normal appearing lymphoid nodules. Some are small while others are large with germinal centers.

ANIMAL ID: D01095
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/27 4/25 6/19 8/18 12/16 3/05
 DAY: 23- 0 29 84 144 264 344

--HEMATOLOGY--

HCT(Z)	43	47	43	48	40	56	46
HGB(GX)	15.5	16.8	15.6	16.0	15.6	17.7	16.4
RBC(10 ⁶ /CHM)	6.02	6.55	6.33	6.64	6.05	7.69	6.96
WBC(10 ³ /CHM)	8.57	9.60	8.51	10.81	10.13	8.27	6.98
NEUT,I(XWBC)	0.0	0.0	3.0	0.0	0.0	0.0	0.0
NEUT,M(XWBC)	70.0	55.0	60.0	58.0	58.0	52.0	51.0
NEUT,M(10 ³)	6.00	5.28	5.11	6.27	6.79	4.30	3.56
LYMPHO(XWBC)	23.0	36.0	28.0	37.0	35.0	37.0	47.0
LYMPHO(10 ³)	1.97	3.46	2.38	4.00	4.10	3.06	3.28
MONO(XWBC)	6.0	2.0	6.0	0.0	1.0	6.0	1.0
EOSINO(XWBC)	1.0	9.0	3.0	5.0	6.0	5.0	1.0
BASO(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(XWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(XRBC)	1.7	0.4	0.5	1.1	1.1	1.3	0.6
THR(10 ⁴ /CHM)	45	36	23	16	21	26	25
PROTIME(SEC)	5.9	9.4	6.9	7.4	7.4	6.4	8.9

--BLOOD CHEM--

BUN(MGZ)	12.7	14.6	19.7	11.5	14.8	17.7	22.8
BS(MGZ)	87	91	83	82	88	82	66
AP(KAU)	2.8	4.2	4.3	3.6	2.2	2.2	5.8
SGOT(RFU/ML)	11	16	17	19	11	14	26
SGPT(RFU/ML)	18	16	18	16	13	17	18
BILI(MGZ)							
CL-(MEQ/L)	121	115	115	114	110	115	115
CA++(MGZ)	9.8	10.2	10.6	9.8	10.6	10.4	10.6
PCO2(MEQ/L)	24.0	23.8	24.8		21.8	19.8	24.5
PH	7.340	7.328	7.370		7.360	7.349	7.337
PROTEIN(GZ)	6.90	6.30					6.80
PCO2(MMHG)	43.3	43.9	41.6		36.9	34.6	44.8

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1095

Dose Level (Mg/Day): 1

Necropsy Date: 24 March 1976

Day: 364

Sampling Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin						
-3	7.1	2.8	4.3	0.658	1.0	0.8	1.0	0.8	0.3
0	6.3	-	-	-	-	-	-	-	-
13	6.4	4.3	2.1	2.024	0.2	0.7	0.8	0.1	0.2
20	7.5	3.0	4.5	0.670	0.9	1.3	0.4	1.1	0.8
39	6.6	3.7	2.9	1.310	0.8	0.5	0.3	0.7	0.5
50	7.6	3.7	3.9	0.973	2.1	0.0	1.1	0.5	0.2

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Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
4.02	5.40

Bile
0.207

URINALYSIS

ANIMAL NUMBER.		(A/3-10)	D1095M
DAY ONE DATE			032775
INITIAL BODY WEIGHT.			9.7 Kg
FINAL BODY WEIGHT			

COMPOUND	DOSE	ROUTE	HCb	mg/dog/day	oral
1	2	3	4	5	6

Treatment Date	A(U/11-16)	042675	062375	082175	121775	030576
Day in Study	I(U/17-19)	30	88	147	266	345
Sp. Gr.	R(U/20-24)	1.060	1.045	1.045	1.064	1.062
pH	R(U/25-28)	6	9	6	6	5.5
Sugar	I(U/30-34)	0	0	0	0	
Ketones	I(U/35-38)	0	0	0	0	
Blood	I(U/40-44)	0	0	0	trace	trace
Protein	I(U/45-49)	1+	1+	trace	2+	1+

		MICROSCOPIC	
Triple Phosphates	I(U/20-24)		
Uric Acid	I(U/25-28)		
Calcium Salts	I(U/30-34)		
Other	A(U/35-38)	bact.	sperm
Casts/LPF 100X (Avg/Field)	I(U/40-44)	0	waxy
RBC/HPF 400X (Avg/Field)	I(U/45-49)	0	0
WBC/HPF 400X (Avg/Field)	I(U/50-54)	1-6	*
EPITH/HPF 400X (Avg/Field)	I(U/55-59)	mod,	0-3
Mucous	I(U/60-68)		
Appearance	I(U/70-80)	brown yellow	cl y cl dky cldky

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1095M</u>	NECROPSY DATE	<u>3/24/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>9:50 AM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/24/76</u>
PATHOLOGY NUMBER	<u>76-2032</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>362</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: + lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the gastric mucosa at the junction of the body and pyloric antrum there are approximately 12, 3 mm nodules.

MICROSCOPIC OBSERVATIONS:

Stomach, pyloric-antrum: Visible in the mucosa were a moderate number of small and medium size lymphoid nodules.

ANIMAL ID: D01099
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	23-	0	29	84	144	264	344
---HEMATOLOGY---							
HCT(Z)	38	41	40	47	46	53	44
HGLB(GZ)	13.6	14.8	14.5	16.0	17.1	16.4	16.5
RBC(10 ¹⁶ /CMM)	5.09	5.65	5.63	6.61	6.54	6.97	6.83
WBC(10 ¹³ /CMM)	9.48	10.09	8.75	11.66	9.42	12.06	10.09
NEUT,I(ZWBC)	0.0	0.0	1.0	0.0	0.0	1.0	0.0
NEUT,M(ZWBC)	61.0	46.0	65.0	67.0	59.0	62.0	63.0
NEUT,M(10 ¹³)	5.78	4.64	5.69	7.81	5.56	7.48	6.36
LYMPHO(ZWBC)	29.0	43.0	26.0	22.0	33.0	34.0	33.0
LYMPHO(10 ¹³)	2.75	4.34	2.28	2.57	3.11	4.10	3.33
MONO(ZWBC)	3.0	0.0	3.0	0.0	2.0	1.0	1.0
EOSINO(ZWBC)	7.0	11.0	5.0	11.0	6.0	2.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.2	0.4	1.0	1.2	2.1	1.8	0.8
THR(10 ¹⁴ /CMM)	45	33	24	22	21	15	29
PROTIME(SEC)	6.4	7.4	6.4	6.9	8.0	6.9	8.1

---BLOOD CHEM---

BUN(MGZ)	16.2	17.9	16.6	17.1	15.5	18.3	16.1
BS(MGZ)	83	77	70	71	74	73	65
AP(KAU)	4.5	3.6	3.0	2.1	1.5	1.7	1.4
SGOT(RFU/ML)	15	13	11	16	11	17	12
SGPT(RFU/ML)	22	15	15	14	12	22	15
BILI(MGZ)							
CL-(MEQ/L)	122	114	110	116	105	116	117
CA++(MGZ)	10.2	10.4	10.4	10.4	11.2	10.2	10.0
PCO2(MEQ/L)	26.2	26.5	27.8	28.8	22.2	20.2	25.5
PH	7.349	7.381	7.393	7.387	7.357	7.370	7.375
PROTEIN(GZ)	6.20	5.80			38.8	34.0	6.50
PCO2(MMHG)	46.5	43.9	44.3	46.9			42.5

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1099

Dose Level (Mg/Day): 1

Necropsy Date: 24 March 1976

Day: 364

Sampling Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin							
-3	7.7	3.0	4.7		0.636	1.3	1.0	1.0	0.8	0.6
0	5.8	2.4	3.4		0.730	0.8	0.8	0.7	0.8	0.4
13	6.9	4.7	2.2		2.095	0.3	0.5	1.1	0.0	0.3
20	8.2	3.2	5.0		0.640	0.8	1.7	0.9	0.6	1.0
39	7.0	3.9	3.1		1.286	1.3	0.0	1.3	0.0	0.4
50	6.8	4.4	2.4		1.787	0.8	0.0	1.2	0.0	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Total</u>	<u>Lipid Extract</u>
3.53	4.04

Bile
0.223

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1099MANIMAL NUMBER. (A/3-10) D1099M

DAY ONE DATE 032775

INITIAL BODY WEIGHT.	10.5 Kg
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FINAL BODY WEIGHT

COMPOUND	HCB
DOSE	1 mg/dog/day

COMPOUND	HCB
DOSE	1 mg/dog/day

ROUTE oral

Treatment Date	A(AU/11-16)	042675	062375	5082175	121775	030576
Day in Study	I(U/17-19)	30	88	147	266	345
Sp. Gr.	R(U/20-24)	1.063	1.038	1.055	1.064	1.062
pH	R(U/25-29)	6	9	6	6	6
Sugar	I(U/30-34)	0	0	0	0	0
Ketones	I(U/35-39)	0	0	0	0	0
Blood	I(U/40-44)	0	0	0	0	0
Protein	I(U/45-49)	1+	trace	trace	2+	1+

		MICROSCOPIC	
Triple Phosphates	I(U/20-24)	4+	2+
Uric Acid	I(U/25-29)		
Calcium Salts	I(U/30-34)	4+	
Other	A(U/35-39)	art.	sperm
Casts/LPF 100X (Avg/Field)	I(U/40-44)	0	gran. sperm
RBC/HPF 400X (Avg/Field)	I(U/45-49)	0	hyaline 1-2
WBC/HPF 400X (Avg/Field)	I(U/50-54)	0	0 2-3 1-2
EPITH/HPF 400X (Avg/Field)	I(U/55-59)	0	0 2-3 1-2
Mucous	I(U/60-69)	0-4	0-2 4-5 1-2
Appearance	I(U/70-80)	brown yellow	yellow cl d k y cld k y

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1099M</u>	NECROPSY DATE	<u>3/24/76</u>
DATE ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>11:25 AM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/24/76</u>
PATHOLOGY NUMBER	<u>76-2083</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>362</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01101
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 11
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	21-	0	29	84	144	264	344
--HEMATOLOGY--							
HCT(%)	44	41	41	44	35	47	44
HGB(GZ)	15.9	14.1	14.5	13.9	15.1	15.4	16.2
RBC(10 ¹⁶ /CMM)	6.13	5.65	5.95	6.15	5.98	6.79	7.11
WBC(10 ¹³ /CMM)	14.37	8.26	8.42	8.02	8.42	6.92	8.77
NEUT,I(%)	1.0	0.0	0.0	0.0	0.0	0.0	0.0
NEUT,M(%)	59.0	58.0	52.0	67.0	63.0	68.0	57.0
NEUT,L(%)	8.48	4.79	4.38	5.37	5.30	4.71	5.00
LYMPHO(%)	35.0	37.0	45.0	32.0	36.0	30.0	42.0
LYMPHO(10 ¹³ /CMM)	5.03	3.06	3.79	2.57	3.03	2.08	3.68
MONO(%)	3.0	3.0	2.0	0.0	1.0	0.0	0.0
EOSINO(%)	2.0	2.0	1.0	1.0	0.0	2.0	1.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	0.7	0.5	0.4	0.3	0.7	0.5	0.3
THR(10 ¹⁴ /CMM)	29	44	69	18	25	24	35
PROTIME(SEC)	6.4	7.9	6.4	6.9	8.6	7.4	7.9

---BLOOD CHEM---

BUN(MGZ)	17.8	19.0	13.4	15.5	22.7	17.7	16.0
BS(MGZ)	73	83	73	70	72	74	69
AP(KAU)	4.5	4.3	7.3	3.0	2.2	2.8	2.4
SGOT(RFU/ML)	19	16	15	15	13	15	17
SGPT(RFU/ML)	15	11	15	12	14	13	13
BILI(MGZ)							
CL-(MEQ/L)	115	112	114	111	110	113	116
CA++(MGZ)	10.0	10.0	10.2	10.6	11.0	10.6	10.2
PCO2(MEQ/L)	19.2	25.2	25.5	25.8	22.5	21.8	23.2
PH	7.205	7.331	7.325	7.340	7.353	7.302	7.285
PROTEIN(GZ)	6.80	6.30					6.50
PCO2(MMHG)	46.3	46.2	47.7	46.2	39.4	41.5	47.1

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1101

Dose Level (Mg/Day): 1

Necropsy Date: 25 March 1976

Day: 365

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.6	2.4	4.2	0.587	1.0	0.9	0.6	0.8	0.8
0	6.3	2.5	3.8	0.659	1.2	0.7	0.8	0.6	0.5
13	-	-	-	-	-	-	-	-	-
20	6.8	3.1	3.7	0.835	0.6	1.1	0.5	0.7	0.8
39	6.6	4.0	2.6	1.509	0.6	0.7	1.0	0.0	0.3
50	6.0	3.7	2.3	1.619	0.8	0.0	1.2	0.0	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
Bile	Lipid Extract
0.733	18.04
	21.58

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1101M</u>	NECROPSY DATE	<u>3/25/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>8:40 AM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/25/76</u>
PATHOLOGY NUMBER	<u>76-2086</u>	POSTMORTEM STATE	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM INTERVAL	<u>Excellent</u>
AGE	<u>22 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>363</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, cardia, body, pyloric antrum: +++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa in the area of the pyloric antrum is covered with 2 mm nodules. A small number are present in the body of the stomach along the lesser curvature and about 6 are near the cardia.

MICROSCOPIC OBSERVATIONS:

Stomach, body, lesser curvature: Visible in the mucosa are a small number of small and medium size lymphoid nodules.

Esophagus-cardia: Visible in the mucosa of the cardia are a small number of lymphoid nodules.

Stomach, pyloric antrum: Visible in the mucosa are numerous small and medium size lymphoid nodules. These nodules extend down into the area of the pyloric canal.

ANIMAL ID: D01106
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 0
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/06	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	21-	0	29	84	144	264	344
--HEMATOLOGY--							
HCT(%)	41	43	44	40	40	46	40
HGB(GZ)	14.8	16.0	16.0	13.9	15.9	16.1	15.5
RBC(10 ¹⁶ /CMM)	5.13	5.93	5.91	5.43	5.88	6.21	6.44
WBC(10 ¹³ /CMM)	13.10	11.51	12.89	10.34	9.82	9.60	7.77
NEUT,I(%WBC)	0.0	0.0	3.0	1.0	0.0	1.0	1.0
NEUT,M(%WBC)	56.0	47.0	51.0	36.0	56.0	58.0	41.0
NEUT,M(10 ¹³)	7.34	5.41	6.57	3.72	5.50	5.57	3.19
LYMPHO(%WBC)	43.0	36.0	34.0	47.0	33.0	34.0	56.0
LYMPHO(10 ¹³)	5.63	4.14	4.38	4.86	3.24	3.26	4.35
MONO(%WBC)	1.0	2.0	2.0	1.0	4.0	2.0	0.0
EOSINO(%WBC)	0.0	15.0	10.0	15.0	7.0	5.0	2.0
BASO(%WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(%WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%RBC)	1.2	0.6	0.8	0.6	1.1	1.5	0.1
THR(10 ¹⁴ /CMM)	36	37	32	17	29	32	31
PROTIME(SEC)	7.4	8.9	6.9	7.0	8.9	8.4	8.4

--BLOOD CHEM--

BUN(MGZ)	20.0	19.6	14.1	19.2	15.3	14.6	15.0
BS(MGZ)	96	102	86	89	82	88	79
AP(KAU)	4.5	3.7	3.6	4.6	5.2	3.3	2.8
SGOT(RFU/ML)	15	13	17	15	16	16	15
SGPT(RFU/ML)	13	15	14	13	14	12	16
BILI(MGZ)							
CL-(MEQ/L)	111	116	113	112	111	115	110
CA++(MGZ)	10.6	10.2	10.4	10.2	9.4	10.4	10.0
PCO2(MEQ/L)	21.0	25.2	25.2	22.8	22.2	19.5	20.8
PH	7.318	7.279	7.350	7.330	7.300	7.345	7.350
PROTEIN(GZ)	6.40	6.20					6.60
PCO2(MMHG)	40.0	52.7	44.9	41.9	43.8	34.6	36.7

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1106

Dose Level (Mg/Day): 1

Necropsy Date: 30 March 1976

Day: 370

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	6.5	2.4	4.1	0.601	1.1	0.6	0.7	0.9	0.7
0	6.2	2.1	4.1	0.520	1.0	1.0	0.7	0.7	0.8
13									
20	7.6	3.5	4.1	0.832	0.7	1.3	0.6	0.8	0.7
39	6.5	4.2	2.3	1.789	0.7	0.6	0.4	0.4	0.3
50	7.1	4.5	2.6	1.688	0.6	0.8	0.8	0.0	0.4

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Tissue HCB (PPM) Level at Necropsy

Fat	
Bile	
0.198	
Total	Lipid Extract
4.72	5.93

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1106F</u>	NECROPSY DATE	<u>3/30/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>11:30</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/30/76</u>
PATHOLOGY NUMBER	<u>76-2087</u>	PRENECROPSY CONDITION	<u>Good</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>368</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, body-pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa in the area of the pyloric antrum is covered with about 100, 1-3 mm nodules. A small number extend into the pyloric canal.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are a few very small and moderate sized lymphoid nodules.

ANIMAL ID: D01111
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/17	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	10-	0	29	84	144	264	344
--HEMATOLOGY--							
HCT(%)	43	40	42	48	46	55	54
HGB(GX)	15.3	14.4	15.0	16.3	18.3	19.4	17.2
RBC(10 ¹⁶ /CMM)	6.35	6.31	6.17	6.98	7.02	7.94	7.81
WBC(10 ¹³ /CMM)	10.18	8.35	6.70	8.09	10.62	8.22	6.11
NEUT,I(ZWBC)	1.0	0.0	0.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	56.0	44.0	45.0	48.0	60.0	50.0	58.0
NEUT,M(10 ¹³)	5.70	3.67	3.02	3.88	6.37	4.11	3.54
LYMPHO(ZWBC)	26.0	47.0	45.0	51.0	33.0	42.0	36.0
LYMPHO(10 ¹³)	2.65	3.92	3.02	4.13	3.50	3.45	2.20
MONO(ZWBC)	5.0	1.0	4.0	0.0	4.0	2.0	0.0
EOSINO(ZWBC)	12.0	8.0	6.0	1.0	3.0	6.0	6.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.9	0.4	0.7	1.3	1.4	0.7	0.3
THR(10 ¹⁴ /CMM)	28	17	21	15	16	25	30
PROTIME(SEC)	8.9	8.4	7.0	6.4	7.5	7.4	7.4

--BLOOD CHEM--

BUN(MGX)	17.0	17.1	10.9	18.9	15.4	16.8	22.6
BS(MGX)	93	87	89	81	100	88	80
AP(KAU)	4.3	3.1	4.0	2.6	1.9	1.8	1.8
SGOT(RFU/ML)	18	16	18	17	14	18	19
SGPT(RFU/ML)	18	12	17	12	17	18	17
BILI(MGX)							
CL-(MEQ/L)	116	117	115	114	110	116	114
CA++(MGX)	11.3	11.2	10.6	10.0	9.8	10.2	10.2
PCO2(MEQ/L)	22.5	25.6	25.0	25.0	22.8	16.2	22.8
PH	7.292	7.357	7.338	7.385	7.184	7.296	7.375
PROTEIN(GX)	6.80	6.50					6.40
PCO2(MMHG)	45.0	44.1	45.1	40.3	58.2	31.2	37.5

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1111

Dose Level (Mg/Day): 1

Necropsy Date: 25 March 1976

Day: 363

Sampling Time (Weeks)	Protein	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
		Albumin	Globulin							
-3	-	-	-	-	-	-	-	-	-	-
0	6.5	3.4	3.1	1.070	0.4	0.6	0.9	0.7	0.6	0.6
13	-	-	-	-	-	-	-	-	-	-
20	7.7	3.2	4.5	0.709	0.8	1.2	0.3	1.3	0.9	0.9
39	6.5	4.1	2.4	1.654	0.5	0.7	1.0	0.0	0.3	0.3
50	6.7	4.8	1.9	2.565	0.3	0.4	0.2	0.7	0.2	0.2

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
1.088	30.03	42.83

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1111M</u>	NECROPSY DATE	<u>3/25/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>1:30 PM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/25/76</u>
PATHOLOGY NUMBER	<u>76-2089</u>	PRENECROPSY CONDITION	<u>Good</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>363</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: In the gastric mucosa of the pyloric antrum there are about 150, 2 mm nodules. A small number are present in the pyloric canal.

MICROSCOPIC OBSERVATIONS:

Stomach, pyloric antrum: Visible in the mucosa are a small number of moderate sized lymphoid nodules.

ANIMAL ID: D01116
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/27/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 0.100000
 (MG/DOG): 1.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: CAPSULE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/17	3/27	4/25	6/19	8/18	12/16	3/05
DAY:	10-	0	29	84	144	264	344
--HEMATOLOGY--							
HCT(%)	51	46	46	50	42	57	46
HGB(GZ)	18.6	17.4	16.8	16.9	16.3	18.8	17.4
RBC(10 ¹⁶ /CMM)	6.96	6.69	6.25	6.61	6.01	7.57	7.29
WBC(10 ¹³ /CMM)	8.22	6.55	5.95	10.74	7.48	9.87	8.64
NEUT,I(ZWBC)	0.0	0.0	1.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	50.0	43.0	38.0	60.0	53.0	54.0	66.0
NEUT,M(10 ¹³)	4.11	2.82	2.26	6.44	3.96	5.33	5.70
LYMPHO(ZWBC)	37.0	47.0	48.0	28.0	37.0	30.0	29.0
LYMPHO(10 ¹³)	3.04	3.08	2.86	3.01	2.77	2.96	2.51
MONO(ZWBC)	3.0	2.0	5.0	5.0	3.0	8.0	0.0
EOSINO(ZWBC)	10.0	8.0	8.0	7.0	7.0	8.0	5.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.7	0.2	0.5	0.6	1.2	0.6	0.9
THR(10 ¹⁴ /CMM)	33	37	26	20	25	27	32
PROTIME(SEC)	6.9	8.9	6.4	6.0	7.4	6.4	7.4

--BLOOD CHEM--

BUN(MGZ)	14.8	13.0	11.7	12.9	13.8	15.3	17.0
BS(MGZ)	103	83	77	73	77	75	66
AP(KAU)	3.9	2.9	3.0	2.4	3.0	1.6	1.9
SGOT(RFU/ML)	19	15	13	14	16	14	16
SGPT(RFU/ML)	29	17	18	14	14	16	14
BILI(MGZ)							
CL-(MEQ/L)	113	111	115	110	113	119	117
CA++(MGZ)	9.8	10.2	10.0	10.2	10.2	10.6	9.8
PCO2(MEQ/L)	23.8	27.8	25.8	26.2	22.8	20.5	25.0
PH	7.241	7.346	7.392	7.350	7.300	7.355	7.392
PROTEIN(GZ)	6.60	5.80					6.60
PCO2(MMHG)	53.9	49.8	41.3	46.3	44.8	35.7	39.9

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1116

Dose Level (Mg/Day): 1

Necropsy Date: 25 March 1976

Day: 365

Sampling Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
		Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	5.8	2.6	3.2	0.806	0.9	0.8	0.6	0.7	0.3
13	-	-	-	-	-	-	-	-	-
20	7.2	3.2	4.0	0.780	0.8	0.8	0.8	0.8	0.8
39	6.7	4.1	2.6	1.571	0.8	0.0	0.4	1.0	0.4
50	6.8	3.9	2.9	1.328	1.1	0.0	1.3	0.0	0.6

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Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile	0.956	
	29.51	46.18

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1116F
DAY ONE DATE		032775
INITIAL BODY WEIGHT		8.5 Kg
FINAL BODY WEIGHT		

COMPOUND	HCB
DOSE	1 mg/dog/day
ROUTE	oral

Treatment Date	A(UA/11-16)	042875	062375	082175	121775	030576
Day in Study	I(AU/17-19)	32	88	147	266	345
Sp. Gr.	R(U1/20-24)	1.060	1.020	1.060	1.062	1.064
pH	R(U1/25-29)	8	9	6	6	6
Sugar	I(U1/30-34)	0	0	0	0	0
Ketones	I(U1/35-39)	0	0	0	0	0
Blood	I(U1/40-44)	0	mod.	0	0	2+
Protein	I(U1/45-49)	1+	1+	trace	1+	2+

		MICROSCOPIC	
Triple Phosphates	I(U2/20-24)		
Uric Acid	I(U2/25-29)		
Calcium Salts	I(U2/30-34)	1+	
Other	A(U2/35-39)	art.	
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-1	0-1
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-2	0-1
Mucous	I(U2/60-69)		
Appearance	I(U2/70-80)	yellow	cl dk y cl dk y

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1116F</u>	NECROPSY DATE	<u>3/25/76</u>
DAY ONE DATE	<u>3/27/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:40 AM</u>
DOSE Mg/Da	<u>1</u>	DATE DIED	<u>3/25/76</u>
PATHOLOGY NUMBER	<u>76-2088</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>20 mo</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND NECROPSY DAY			<u>363</u>

SUMMARY:

DRUG INDUCED LESIONS

Stomach, pyloric antrum-canal: ++ lymphoid hyperplasia

OBSERVATIONS:

Digestive System: The gastric mucosa in the area of the pyloric antrum is covered by 2 mm nodules. Some of these nodules extend into the pyloric canal.

MICROSCOPIC OBSERVATIONS:

Stomach, body-pyloric antrum: Visible in the mucosa are numerous medium and large sized lymphoid nodules.

ANIMAL ID: D01081
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 0
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/28 5/02 6/20 8/19
 DAY: 25- 0 35 84 144

--HEMATOLOGY--

HCT(%)	42	44	50	49	46
HGB(GZ)	14.8	16.0	16.5	16.7	16.3
RBC(10 ¹⁶ /CMM)	5.60	6.12	5.32	6.72	6.52
WBC(10 ¹³ /CMM)	8.78	7.67	5.06	6.08	8.00
NEUT,I(2WBC)	2.0	0.0	2.0	1.0	0.0
NEUT,M(2WBC)	58.0	55.0	51.0	44.0	49.0
NEUT,M(10 ¹³)	5.09	4.22	2.58	2.68	3.92
LYMPHO(2WBC)	35.0	40.0	36.0	45.0	46.0
LYMPHO(10 ¹³)	3.07	3.07	1.82	2.74	3.68
MONO(2WBC)	3.0	3.0	2.0	0.0	0.0
EOSINO(2WBC)	2.0	2.0	9.0	10.0	5.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0
RET(2RBC)	0.5	0.4	0.7	1.7	1.2
THR(10 ¹⁴ /CMM)	29	26	20	12	18
PROTIME(SEC)	8.5	9.9	6.9	8.9	7.6

--BLOOD CHEM--

BUN(MGZ)	26.8	17.1	16.3	20.2	14.6
BS(MGZ)	104	104	100	91	93
AP(KAU)	2.1	3.3	2.0	2.8	1.6
SGOT(RFU/ML)	21	13	17	17	15
SGPT(RFU/ML)	21	16	17	16	13
BILI(MGZ)					
CL-(MEQ/L)	116	114	113	116	110
CA++(MGZ)	10.0	10.6	10.4	10.4	10.6
PCO2(MEQ/L)	23.0	24.8	22.2	22.5	22.0
PH	7.368	7.392	7.410	7.363	7.410
PROTEIN(GZ)	5.90	5.70			
PCO2(MMHG)	38.6	39.5	34.1	38.3	33.4

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1081 Necropsy Date: 20 August 1975
 Dose Level (Mg/Day): 0 Day: 146

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Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	$\frac{\alpha-1}{\alpha-2}$	$\frac{\beta-1}{\beta-2}$	γ
	Protein	Albumin	Globulin				
-3	7.6	3.0	4.6	0.648	1.4	1.0	0.6
0	5.7	3.1	2.6	1.214	0.5	0.5	0.5
13	6.3	5.0	1.3	3.778	0.1	0.3	0.1
20	7.4	3.1	4.3	0.739	0.7	1.3	1.0
39				Sacrificed			
50							

Sacrificed

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Tissue HCB (PPM) Level at Necropsy

	Fat	
	<u>Total</u>	<u>Lipid Extract</u>
Bile	< .01	< .01

URINALYSIS

ANIMAL NUMBER.	. . .	(A/3-10)	D1081M
DAY ONE DATE	. . .	.	032875
INITIAL BODY WEIGHT.	. . .	.	10.2 Kg
FINAL BODY WEIGHT	. . .	.	10.5 Kg

COMPOUND	.	.	.	.	.	HCB
DOSE	.	.	.	.	.	. Control
ROUTE	.	.	.	.	.	. oral

[illegible]

*** Too numerous to count**

ANIMAL ID: D01072
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/29/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.00000
 (MG/DOG): 0.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/03 3/28 5/02 6/20 8/19
 DAY: 26- 1 34 83 143

--HEMATOLOGY--

HCT(%)	50	47	55	57	52
HGB(GZ)	17.5	17.0	18.3	18.2	17.1
RBC(10 ¹⁶ /CMM)	6.72	6.72	6.35	7.72	7.33
WBC(10 ¹³ /CMM)	12.80	10.86	6.44	11.04	11.58
NEUT,I(ZWBC)	0.0	0.0	3.0	0.0	0.0
NEUT,M(ZWBC)	64.0	55.0	57.0	62.0	61.0
NEUT,M(10 ¹³)	8.19	5.97	3.67	6.84	7.06
LYMPHO(ZWBC)	32.0	43.0	35.0	32.0	29.0
LYMPHO(10 ¹³)	4.10	4.67	2.25	3.53	3.36
MONO(ZWBC)	3.0	0.0	2.0	6.0	3.0
EOSINO(ZWBC)	1.0	2.0	3.0	0.0	7.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.6	0.1	0.5	0.5	0.3
THR(10 ¹⁴ /CMM)	33	38	21	25	26
PROTIME(SEC)	8.4	10.9	8.9	8.4	8.9

--BLOOD CHEM--

BUN(MGZ)	16.3	16.4	11.2	17.9	13.9
BS(MGZ)	77	92	68	67	79
AP(KAU)	3.9	3.5	2.5	2.2	2.1
SGOT(RFU/ML)	18	13	15	14	11
SGPT(RFU/ML)	21		21	18	12
BILI(MGZ)					
CL-(MEQ/L)	116		112	112	112
CA++(MGZ)	10.6		10.6	10.4	10.6
PCO2(MEQ/L)	21.5		23.8	23.8	22.2
PH	7.352	7.364	7.345	7.295	7.370
PROTEIN(GZ)	5.90	5.70			
PCO2(MMHG)	37.6	43.0	42.1	47.1	37.1

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1072 Necropsy Date: 20 August 1975
 Dose Level (Mg/Day): 0 Day: 146

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	<u>a-1</u>	<u>a-2</u>	<u>β-1</u>	<u>β-2</u>	<u>γ</u>
	Protein	Albumin	Globulin						
-3	6.6	2.8	3.8	0.724	1.3	0.7	1.0	0.5	0.3
0	5.7	-	-	-	-	-	-	-	-
13	-	-	-	-	-	-	-	-	-
20	7.7	3.3	4.4	0.745	0.9	1.3	1.3	-	0.9
39									
50									

Sacrificed

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
<.01	0.12	0.14

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1072F

ANIMAL NUMBER. . . . (A/3-10) D1072F

DAY ONE DATE 032875

INITIAL BODY WEIGHT.		8.3 Kg
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FINAL BODY WEIGHT	8.78 Kg
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COMPOUND	HCB
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DOSE	Control
0	100
1	100
2	100
3	100
4	100
5	100
6	100
7	100
8	100
9	100
10	100
11	100
12	100
13	100
14	100
15	100
16	100
17	100
18	100
19	100
20	100
21	100
22	100
23	100
24	100
25	100
26	100
27	100
28	100
29	100
30	100
31	100
32	100
33	100
34	100
35	100
36	100
37	100
38	100
39	100
40	100
41	100
42	100
43	100
44	100
45	100
46	100
47	100
48	100
49	100
50	100
51	100
52	100
53	100
54	100
55	100
56	100
57	100
58	100
59	100
60	100
61	100
62	100
63	100
64	100
65	100
66	100
67	100
68	100
69	100
70	100
71	100
72	100
73	100
74	100
75	100
76	100
77	100
78	100
79	100
80	100
81	100
82	100
83	100
84	100
85	100
86	100
87	100
88	100
89	100
90	100
91	100
92	100
93	100
94	100
95	100
96	100
97	100
98	100
99	100
100	100

ROUTE oral

Treatment Date	A(AU/11-16)	050275	062375	082075
Day in Study	I(AU/17-19)	35	87	145
Sp. Gr.	R(U1/20-24)	1.045	1.045	1.050
pH	R(U1/25-29)	8	8	6
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	trace	trace	trace
REAGENT STRIP				
MICROSCOPIC				
Triple Phosphates	I(U2/20-24)	4+	2+	
Uric Acid	I(U2/25-29)	0		
Calcium Salts	I(U2/30-34)	0		
Other	A(U2/35-39)	0		
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0	0	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-2	5-10	0-2
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	2-8	0-5	5-10
Mucous	I(U2/60-69)			
Appearance	I(U2/70-80)	yellow	yellow	yellow

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1081M</u>	NECROPSY DATE	<u>8/20/75</u>
DAY ONE DATE	<u>3/28/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:25 AM</u>
DOSE Mg/Da	<u>0</u>	DATE DIED	<u>8/20/75</u>
PATHOLOGY NUMBER	<u>75-6079</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>146</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL NUMBER	<u>D1072F</u>	NECROPSY DATE	<u>8/20/75</u>
DAY ONE DATE	<u>3/28/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>8:45 AM</u>
DOSE Mg/Da	<u>0</u>	DATE DIED	<u>8/20/75</u>
PATHOLOGY NUMBER	<u>75-6078</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>146</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01118
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/17 3/28 5/02 6/20 8/19
 DAY: 11- 0 35 84 144

--HEMATOLOGY--

	50	44	47	48	49
HCT(%)	17.2	15.7	16.8	16.5	17.5
HGB(GZ)	7.27	6.13	4.67	6.47	7.25
RBC(10 ¹² /CMM)	10.80	8.67	5.21	9.79	7.96
WBC(10 ³ /CMM)	0.0	0.0	0.0	0.0	0.0
NEUT,I(%)	70.0	58.0	77.0	45.0	59.0
NEUT,M(%)	7.56	5.03	4.01	4.41	4.70
LYMPHO(%)	23.0	34.0	19.0	37.0	35.0
LYMPHO(10 ³ /CMM)	2.48	2.95	0.99	3.62	2.79
MONO(%)	5.0	0.0	0.0	1.0	1.0
EOSINO(%)	2.0	8.0	4.0	17.0	5.0
BASO(%)	0.0	0.0	0.0	0.0	0.0
NORMBL(%)	0.0	0.0	0.0	0.0	0.0
RET(%)	0.3	0.2	1.0	0.4	0.4
THR(10 ⁴ /CMM)	40	46	26	22	22
PROTIME(SEC)	7.0	7.9	7.4	9.5	8.0

--BLOOD CHEM--

	12.0	17.3	14.8	15.7	13.5
BUN(MGZ)	103	84	73	70	82
AP(KAU)	5.0	4.1	4.4	3.7	3.6
SGOT(RFU/ML)	21	15	21	17	13
SGPT(RFU/ML)	15	15	15	15	12
BILI(MGZ)	118	116	114	112	108
CL-(MEQ/L)	10.5	9.8	9.8	9.4	10.2
CA++(MGZ)	23.0	25.8	23.0	21.8	22.0
PCO2(MEQ/L)	7.275	7.360	7.331	7.355	7.340
PH	6.60	6.40			
PROTEIN(GZ)	48.1	44.3	42.1	37.5	39.8
PCO2(MMHG)					

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1118

Dose Level (Mg/Day): 0

Necropsy Date: 22 August 1975

Day: 148

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.4	2.8	3.6	0.775	0.6	0.4	1.0	0.7	0.8
13	-	-	-	-	-	-	-	-	-
20	8.8	2.9	5.9	0.503	0.7	1.5	0.7	1.3	1.6
39									
50									

Sacrificed

Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
<0.1	0.18	0.29

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1118F

DAY ONE DATE 032875

INITIAL BODY WEIGHT.	7.3 Kg
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FINAL BODY WEIGHT

COMPOUND HCB

DOSE	Control
100	100
50	100
25	100
12.5	100
6.25	100
3.125	100
1.5625	100
0.78125	100
0.390625	100
0.1953125	100
0.09765625	100
0.048828125	100
0.0244140625	100
0.01220703125	100
0.006103515625	100
0.0030517578125	100
0.00152587890625	100
0.000762939453125	100
0.0003814697265625	100
0.00019073486328125	100
0.000095367431640625	100
0.0000476837158203125	100
0.00002384185791015625	100
0.000011920928955078125	100
0.0000059604644775390625	100
0.00000298023223876953125	100
0.000001490116119384765625	100
0.0000007450580596923828125	100
0.00000037252902984619140625	100
0.000000186264514923095703125	100
0.0000000931322574615478515625	100
0.00000004656612873077392578125	100
0.000000023283064365386962890625	100
0.0000000116415321826934814453125	100
0.00000000582076609134674072265625	100
0.000000002910383045673370361328125	100
0.0000000014551915228366851806640625	100
0.00000000072759576141834259033203125	100
0.000000000363797880709171295166015625	100
0.0000000001818989403545856475830078125	100
0.00000000009094947017729282379150390625	100
0.000000000045474735088646411895751953125	100
0.0000000000227373675443232059478759765625	100
0.00000000001136868377216160297393798828125	100
0.000000000005684341886080801486968994140625	100
0.0000000000028421709430404007434844970703125	100
0.00000000000142108547152020037174224853515625	100
0.000000000000710542735760100185871124267578125	100
0.0000000000003552713678800500929355621337890625	100
0.00000000000017763568394002504646778106689453125	100
0.000000000000088817841970012523233890533447265625	100
0.0000000000000444089209850062616169452667236328125	100
0.00000000000002220446049250313080847263336181640625	100
0.000000000000011102230246251565404236316680908203125	100
0.0000000000000055511151231257827021181583340541015625	100
0.00000000000000277555756156289135105907916702705078125	100
0.000000000000001387778780781445675529539583513525390625	100
0.0000000000000006938893903907228377647697917567626953125	100
0.00000000000000034694469519536141888238489587838134765625	100
0.000000000000000173472347597680709441192447939190673828125	100
0.0000000000000000867361737988403547205962239695953369140625	100
0.00000000000000004336808689942017736029811198479766845703125	100
0.000000000000000021684043449710088680149055992398834228515625	100
0.00000000000000001084202172485504434007452799619941711428125	100
0.000000000000000005421010862427522170037263998099708557140625	100
0.0000000000000000027105054312137610850186319990498542785703125	100
0.00000000000000000135525271560688054250931599952492713928515625	100
0.0000000000000000006776263578034402712546579997624635696428125	100
0.00000000000000000033881317890172013562732899988123178482140625	100
0.000000000000000000169406589450860067813664499940615892410703125	100
0.0000000000000000000847032947254300339068322499703079462053515625	100
0.00000000000000000004235	

ROUTE **oral**

Treatment Date	AIAU(11-16)	050275	062375	082075
Day in Study	I(AU/17-19)	35	87	145
Sp. Gr.	R(U1/20-24)	1.035	1.017	1.035
pH	R(U1/25-29)	7	7	6
Sugar	I(U1/30-34)	0	0	0
Ketones	I(U1/35-39)	0	0	0
Blood	I(U1/40-44)	0	0	0
Protein	I(U1/45-49)	trace	0	0

		MICROSCOPIC	
Triple Phosphates	I(U2/20-24)		
Uric Acid	I(U2/25-29)	3+	
Calcium Salts	I(U2/30-34)		1+
Other	A(U2/35-39)	art.	
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-1	0
EPI TH/HPF 400X (Avg/Field)	I(U2/55-59)	1-5	2-10
Mucous	I(U2/60-69)		0-3
Appearance	I(U2/70-80)	yellow	lt. y yellow

ANIMAL ID: D01093
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/04 3/28 5/02 6/20 8/19
 DAY: 24- 0 35 84 144

--HEMATOLOGY--

HCT(%)	42	42	50	49	45
HGB(GZ)	15.3	15.3	16.6	16.4	14.7
RBC(10 ⁶ /CMM)	5.71	6.42	5.58	6.72	6.35
WBC(10 ³ /CMM)	8.81	13.29	2.73	10.28	8.02
NEUT,I(ZWBC)	0.0	0.0	0.0	0.0	0.0
NEUT,M(ZWBC)	65.0	54.0	49.0	60.0	56.0
NEUT,M(10 ³)	5.73	7.18	1.34	6.17	4.49
LYMPHO(ZWBC)	32.0	41.0	42.0	28.0	38.0
LYMPHO(10 ³)	2.82	5.45	1.15	2.88	3.05
MONO(ZWBC)	3.0	0.0	4.0	2.0	0.0
EOSINO(ZWBC)	0.0	5.0	5.0	10.0	6.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.9	0.6	1.4	1.6	0.6
THR(10 ⁴ /CMM)	18	29	25	30	33
PROTIME(SEC)	7.4	9.4	7.4	9.9	8.5

--BLOOD CHEM--

BUN(MGZ)	18.6	17.3	11.8	14.9	17.0
BS(MGZ)	105	92	85	75	88
AP(KAU)	7.4	6.1	4.2	5.8	2.7
SGOT(RFU/ML)	28	15	17	11	11
SGPT(RFU/ML)	17	18	14	15	14
BILI(MGZ)					
CL-(MEQ/L)	129	113	112	113	112
CA++(MGZ)	10.4	10.0	9.8	10.4	10.4
PCO2(MEQ/L)	23.8	24.5	22.0	23.2	21.2
PH	7.300	7.292	7.354	7.323	7.360
PROTEIN(GZ)	7.70	5.90			
PCO2(MMHG)	46.5	49.3	38.1	43.4	36.5

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1093 Necropsy Date: 21 August 1975
 Dose Level (Mg/Day): 0 Day: 147

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	5.9	2.4	3.5	0.664	1.3	0.7	0.8	0.5	0.3
13	5.7	4.2	1.5	2.692	0.5	0.0	0.6	0.0	0.5
20	7.4	3.2	4.2	0.746	0.8	1.1	0.8	0.6	0.9
29				Sacrificed					
50									

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
< .01	0.18	0.29

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1118F</u>	NECROPSY DATE	<u>8/21/75</u>
DAY ONE DATE	<u>3/28/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>10:25 AM</u>
DOSE Mg/Da	<u>0</u>	DATE DIED	<u>8/21/75</u>
PATHOLOGY NUMBER	<u>75-6180</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Female</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>148</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL NUMBER	<u>D1093M</u>	NECROPSY DATE	<u>8/21/75</u>
DAY ONE DATE	<u>3/28/75</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
COMPOUND	<u>HCB</u>	HOUR DIED	<u>9:00 AM</u>
DOSE Mg/Da	<u>0</u>	DATE DIED	<u>8/21/75</u>
PATHOLOGY NUMBER	<u>75-6102</u>	PRENECROPSY CONDITION	<u>Excellent</u>
SPECIES	<u>Beagle dog</u>	POSTMORTEM STATE	<u>Excellent</u>
AGE	<u>1 yr.</u>	POSTMORTEM INTERVAL	<u>0</u>
SEX	<u>Male</u>	HOURS REFRIGERATED	<u>0</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>147</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01073
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: 938872
 LOT: 938872
 DAILY DOSE (MG/KG): 0.000000
 (MG/DOG): 0.000000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/03	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	25-	0	35	84	144	257	342
---HEMATOLOGY---							
HCT(%)	43	44	52	49	45	43	48
HGB(GZ)	15.7	15.5	17.1	16.5	16.0	16.3	18.2
RBC(10 ¹⁶ /CMM)	6.12	6.35	5.40	7.07	6.84	6.83	7.72
WBC(10 ¹³ /CMM)	11.41	14.11	2.96	9.69	11.19	10.36	8.29
NEUT,I(2WBC)	2.0	0.0	0.0	3.0	1.0	9.0	3.0
NEUT,M(2WBC)	60.0	64.0	61.0	55.0	66.0	53.0	50.0
NEUT,H(10 ¹³)	6.85	9.03	1.81	5.33	7.39	5.49	4.15
LYMPHO(2WBC)	30.0	26.0	32.0	29.0	26.0	32.0	43.0
LYMPHO(10 ¹³)	3.42	3.67	0.95	2.81	2.91	3.32	3.56
MONO(2WBC)	1.0	2.0	4.0	4.0	1.0	0.0	1.0
EOSINO(2WBC)	7.0	8.0	3.0	9.0	6.0	5.0	3.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0	1.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0	1.0	0.0
RET(ZRBC)	0.6	0.3	0.6	0.6	0.5	0.4	0.0
THR(10 ¹⁴ /CMM)	27	43	18	17	15	18	15
PROTIME(SEC)	7.9	9.9	7.4	8.4	8.9	7.9	8.4

---BLOOD CHEM---

BUN(MGZ)	16.2	18.7	14.0	16.9	14.9	13.7	21.7
BS(MGZ)	73	81	76	80	88	71	74
AP(KAU)	5.0	2.7	2.2	3.1	2.4	2.2	1.6
SGOT(RFU/ML)	17	15	15	15	13	13	15
SGPT(RFU/ML)	35	12	14	14	12	12	15
BILI(MGZ)	115	115	113	111	113	112	115
CL-(MEQ/L)	9.6	10.2	10.2	10.2	10.4	10.2	10.6
CA++(MGZ)	24.2	27.0	24.2	25.2	20.2	25.8	26.2
PCO2(MEQ/L)	7.320	7.367	7.346	7.306	7.372	7.381	7.350
PH	5.90	5.80	43.4	49.3	33.7	42.0	46.7
PROTEIN(GZ)	45.5	46.5					
PCO2(MMHG)							

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1073 Necropsy Date: 11 March 1976
 Dose Level (Mg/Day): 0 Day: 350

Sampling Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin						
-3	6.8	2.6	4.2	0.630	1.0	0.9	0.9	0.8	0.6
0	5.8	2.7	3.1	0.853	0.7	0.6	0.8	0.6	0.5
13	6.4	4.9	1.5	3.211	0.2	0.3	0.9	0.0	0.2
20	7.6	3.3	4.3	0.763	0.9	1.2	0.7	0.8	0.7
39	6.4	4.6	1.8	2.654	0.4	0.4	0.4	0.4	0.1
50	6.5	3.9	2.6	1.469	0.5	0.6	0.5	0.6	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Lipid Extract</u>
0.14	2.71
	3.42

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1073M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/11/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>3:30 PM</u>
PATHOLOGY NUMBER	<u>76-1796</u>	DATE KILLED	<u>3/11/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>22 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>346</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01087
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 0.000000
 (MG/DOG): 0.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/03	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	25-	0	35	84	144	257	342
--HEMATOLOGY--							
HCT(%)	42	42	49	51	49	43	46
HGB(GZ)	15.0	15.4	15.6	17.3	16.1	16.2	17.5
RBC(10 ⁶ /CHM)	5.68	5.93	5.10	6.78	6.76	6.31	6.86
WBC(10 ³ /CHM)	9.04	11.18	5.82	11.47	11.60	13.97	11.25
NEUT,I(ZWBC)	0.0	0.0	3.0	0.0	0.0	1.0	2.0
NEUT,M(ZWBC)	57.0	37.0	53.0	47.0	60.0	57.0	51.0
NEUT,L(10 ³)	5.15	4.14	3.08	5.39	6.96	7.96	5.74
LYMPHO(ZWBC)	30.0	51.0	26.0	38.0	34.0	29.0	41.0
LYMPHO(10 ³)	2.71	5.70	1.51	4.36	3.94	4.05	4.61
MONO(ZWBC)	8.0	0.0	9.0	7.0	1.0	3.0	3.0
EOSINO(ZWBC)	5.0	12.0	9.0	8.0	5.0	9.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	1.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.8	0.5	0.9	1.3	0.9	0.8	0.0
THR(10 ⁴ /CHM)	29	23	17	12	15	15	14
PROTIME(SEC)	8.4	8.9	6.5	8.4	8.0	7.9	8.9

--BLOOD CHEM--

BUN(MGZ)	16.2	19.7	13.2	14.3	14.1	10.1	14.8
BS(MGZ)	91	89	69	64	83	68	71
AP(KAU)	3.7	3.7	2.1	3.6	1.9	1.9	1.3
SGOT(RFU/ML)	14	12	16	15	13	15	15
SGPT(RFU/ML)	18	15	16	13	13	15	17
BILI(MGZ)							
CL-(MEQ/L)	115	113	113	113	110	114	120
CA++(MGZ)	10.0	10.2	10.6	10.4	10.4	10.4	11.0
PCO2(MEQ/L)	21.8	25.8	24.2	25.2	22.0	29.0	25.0
PH	7.343	7.360	7.354	7.335	7.400	7.457	7.343
PROTEIN(GZ)	6.60	6.60					6.40
PCO2(MMHG)	40.4	44.4	42.1	46.0	34.2	40.6	44.8

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1087 Necropsy Date: 11 March 1976
 Dose Level (Mg/Day): 0 Day: 350

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				γ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$
-3	6.9	2.7	4.2	0.657	0.8	1.2	0.8	0.5
0	6.6	3.2	3.4	0.932	0.7	0.6	1.0	0.5
13	6.8	4.8	2.0	2.440	0.2	0.2	0.5	0.5
20	7.6	3.3	4.3	0.763	0.7	1.2	0.9	0.8
39	6.6	4.8	1.8	2.586	0.7	0.0	0.5	0.3
50	6.3	4.2	2.1	2.065	0.5	0.0	0.5	0.3

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Tissue HCB (PPM) Level at Necropsy

Fat	
<u>Bile</u>	<u>Total Lipid Extract</u>
.046	1.11 1.49

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URINALYSIS

ANIMAL NUMBER (A/3-10) D1087M
 DAY ONE DATE 032875
 INITIAL BODY WEIGHT 10.0 Kg
 FINAL BODY WEIGHT
 COMPOUND HCB
 DOSE Control
 ROUTE oral

Treatment Date	050275	062375	082075	121075	030475
Day in Study	35	87	145	250	343
Sp. Gr.	1.036	1.050	1.065	1.062	1.064
pH	9	9	6	6	6
Sugar	0	0	0	0	0
Ketones	0	0	0	0	0
Blood	0	0	0	0	0
Protein	1+	trace	1+	1+	2+

REAGENT STRIP	
A(U/11-19)	050275
I(U/17-19)	35
R(U/20-24)	1.036
R(U/25-29)	9
I(U/30-34)	0
I(U/35-39)	0
I(U/40-44)	0
I(U/45-49)	1+

MICROSCOPIC	
Triple Phosphates	1+
Uric Acid	3+
Calcium Salts	3+
Other	sperm
Casts/LPF 100X (Avg/Field)	0
RBC/HPF 400X (Avg/Field)	0
WBC/HPF 400X (Avg/Field)	0-1
EPITH/HPF 400X (Avg/Field)	0-1
Mucous	yellow/dk. y
Appearance	yellow

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1087M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/11/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>1:30 PM</u>
PATHOLOGY NUMBER	<u>76-1795</u>	DATE KILLED	<u>3/11/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>350</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01088
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE
 (MG/KG): 0.000000
 (MG/DOG): 0.00000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/04	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	9193	0	35	84	144	257	342
--HEMATOLOGY--							
HCT(%)	39	40	47	47	50	45	44
HGB(GZ)	14.2	14.4	15.2	16.3	15.5	16.5	17.1
RBC(10 ¹⁶ /CMM)	4.53	5.66	4.81	7.27	6.47	6.73	6.92
WBC(10 ¹³ /CMM)	10.92	10.10	4.05	9.34	10.49	11.58	12.17
NEUT,I(ZWBC)	0.0	0.0	1.0	0.0	0.0	4.0	1.0
NEUT,M(ZWBC)	74.0	58.0	64.0	42.0	54.0	62.0	63.0
NEUT,M(10 ¹³)	8.08	5.86	2.59	3.92	5.66	7.18	7.67
LYMPHO(ZWBC)	21.0	38.0	30.0	52.0	41.0	33.0	28.0
LYMPHO(10 ¹³)	2.29	3.84	1.22	4.86	4.30	3.82	3.41
MONO(ZWBC)	3.0	2.0	1.0	0.0	0.0	0.0	5.0
EOSINO(ZWBC)	2.0	2.0	4.0	6.0	5.0	1.0	3.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.4	1.3	0.7	1.2	0.8	1.4	0.0
THR(10 ¹⁴ /CMM)	37	39	23	21	20	20	38
PROTIME(SEC)	6.9	8.9	6.4	8.4	7.4	7.9	9.0

--BLOOD CHEM--

BUN(MGZ)	10.8	15.8	10.9	14.5	16.4	12.9	10.8
BS(MGZ)	95	84	76	74	82	80	70
AP(KAU)	10.3	8.4	7.3	5.4	3.1	3.3	2.4
SGOT(RFU/ML)	26	19	20	20	10	22	22
SGPT(RFU/ML)	30	18	15	15	15	20	18
BILI(MGZ)							
CL-(MEQ/L)	120	115	111	115	107	112	112
CA++(MGZ)	10.0	10.2	10.2	10.2	10.8	10.6	10.8
PCO2(MEQ/L)	23.0	27.0	26.3	25.2	21.8	26.5	24.5
PH	7.335	7.355	7.324	7.320	7.343	7.472	7.381
PROTEIN(GZ)	6.20	6.20					7.00
PCO2(MMHG)	41.7	47.6	49.8	47.2	38.8	35.3	40.1

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1088 Necropsy Date: 11 March 1976
 Dose Level (Mg/Day): 0 Day: 350

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)				γ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$
-3	7.3	3.0	4.3	0.700	0.9	0.9	1.2	1.0
0	6.2	2.4	3.8	0.619	0.9	0.6	1.2	0.6
13	6.6	3.9	2.7	1.463	0.4	0.6	0.6	0.6
20	8.3	3.2	5.1	0.642	1.0	1.3	0.9	0.9
39	7.5	4.2	3.3	1.241	0.4	0.0	0.6	2.1
50	7.5	5.0	2.5	1.974	0.3	0.3	0.6	0.9

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
.057	0.99	1.25

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1088F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/11/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>10:30 AM</u>
PATHOLOGY NUMBER	<u>76-1794</u>	DATE KILLED	<u>3/11/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>344</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01108
SPECIES: DOG
SEX: FEMALE
AGE(MO): 0
RX-DATE: 3/28/75
SUPPLIER: MARSHALL

TREATMENT: HCB
LOT: 938872
DAILY DOSE
(MG/KG): 0
(MG/DOG): 0.00000
SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
VEHICLE: LACTOSE
CONCENT(MG/ML): 0.00000

NO GRADES

DATE:	3/06	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	22-	0	35	84	144	257	342
---HEMATOLOGY---							
HCT(%)	48	51	53	47	47	53	57
HGB(GZ)	17.3	18.5	16.9	16.0	16.3	18.9	18.8
RBC(10 ¹⁶ /CMM)	6.21	6.92	5.46	6.34	6.41	7.53	7.50
WBC(10 ¹³ /CMM)	14.50	9.44	3.53	9.72	9.38	8.95	10.68
NEUT,I(%)	0.0	0.0	0.0	0.0	0.0	2.0	1.0
NEUT,M(%)	61.0	49.0	50.0	53.0	46.0	42.0	53.0
NEUT,N(%)	8.85	4.63	1.77	5.15	4.31	3.76	5.66
LYMPHO(%)	38.0	48.0	48.0	41.0	51.0	45.0	46.0
LYMPHO(10 ¹³)	5.51	4.53	1.69	3.99	4.78	4.03	4.91
MONO(%)	1.0	2.0	1.0	0.0	0.0	6.0	0.0
EOSINO(%)	0.0	1.0	1.0	6.0	3.0	5.0	0.0
BASO(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORBL(%)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(%)	1.2	1.0	1.2	1.8	0.6	0.7	0.0
THR(10 ¹⁴ /CMM)	29	23	23	25	11	11	22
PROTIME(SEC)	7.9	11.9	11.9	8.4	7.3	7.4	8.9

---BLOOD CHEM---

BUN(MGZ)	21.6	19.7	17.9	15.1	18.7	19.9	15.5
BS(MGZ)	91	89	80	71	79	78	78
AP(KAU)	4.3	5.1	2.8	4.5	2.8	2.2	1.8
SGOT(RFU/ML)	44	18	17	17	13	17	16
SGPT(RFU/ML)	38	19	18	15	14	18	15
BILI(MGZ)							
CL-(MEQ/L)	117	112	112	110	114	115	115
CA++(MGZ)	10.0	10.4	10.4	9.8	9.8	11.0	10.6
PCO2(MEQ/L)	23.0	26.0	23.2	23.2	22.0	26.2	24.0
PH	7.235	7.284	7.369	7.369	7.320	7.466	7.299
PROTEIN(GZ)	10.50	6.90					6.70
PCO2(MMHG)	52.8	53.9		39.2	41.1	35.2	47.5

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1108 Necropsy Date: 11 March 1976
Dose Level (Mg/Day): 0 Day: 350

Sampling Time (Weeks)	Total		Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
	Albumin	Globulin						
-3	2.4	4.3	0.565	1.3	0.6	0.9	1.0	0.5
0	-	-	-	-	-	-	-	-
13	4.9	1.6	3.067	0.2	0.4	0.9	0.0	0.1
20	3.2	4.6	0.691	0.8	1.1	1.2	0.5	0.9
39	4.2	3.2	1.306	0.6	0.0	0.6	1.7	0.3
50	4.6	2.9	1.592	0.8	0.0	1.7	0.0	0.4

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
.057	0.99	1.25

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1108F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/11/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>8:55 AM</u>
PATHOLOGY NUMBER	<u>76-1793</u>	DATE KILLED	<u>3/11/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>346</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01112
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/17	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	11-	0	35	84	144	257	342
---HEMATOLOGY---							
HCT(%)	41	41	43	45	49	42	49
HGB(GZ)	15.1	14.5	16.0	14.8	17.8	15.2	18.7
RBC(10 ¹⁶ /CMH)	6.60	6.22	4.51	5.99	6.98	6.27	7.63
WBC(10 ¹³ /CMH)	13.16	12.10	5.65	11.64	15.36	23.74	14.99
NEUT,I(2WBC)	0.0	0.0	6.0	2.0	0.0	16.0	3.0
NEUT,M(2WBC)	58.0	59.0	70.0	61.0	74.0	60.0	75.0
NEUT,M(10 ¹³)	7.63	7.14	3.96	7.70	11.37	14.24	11.24
LYMPHO(2WBC)	22.0	30.0	13.0	25.0	24.0	11.0	14.0
LYMPHO(10 ¹³)	2.90	3.63	0.73	3.16	3.69	2.61	2.10
MONO(2WBC)	7.0	2.0	8.0	8.0	1.0	3.0	3.0
EOSINO(2WBC)	16.0	9.0	4.0	3.0	1.0	7.0	5.0
BASO(2WBC)	0.0	0.0	0.0	0.0	0.0	3.0	0.0
NORMBL(2WBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(2RBC)	0.3	0.5	0.7	0.7	0.7	1.1	0.0
THR(10 ¹⁴ /CMH)	51	28	25	15	32	30	34
PROTIME(SEC)	6.9	8.5	7.4	7.9	6.9	6.9	8.4

---BLOOD CHEM---

BUN(MGZ)	17.2	20.7	16.3	20.7	17.9	17.8	12.9
BS(MGZ)	74	84	75	61	77	67	75
AP(KAU)	4.0	4.2	5.1	5.8	4.1	5.6	3.6
SGOT(RFU/ML)	18	15	23	16	13	15	16
SGPT(RFU/ML)	18	14	15	13	12	12	18
BILI(MGZ)							
CL-(MEQ/L)	114	112	113	114	109	111	112
CA++(MGZ)	10.9	10.2	10.4	9.8	11.0	10.4	10.8
PCO2(MEQ/L)	22.5	26.4	25.0	24.8	25.0	31.5	23.8
PH	7.338	7.359	7.365	7.279	7.360	7.456	7.288
PROTEIN(GZ)	6.20	5.60					6.70
PCO2(MMHG)	40.8	45.9	42.3	51.3	49.2	44.0	48.0

Serum Electrophoresis
(All Values = gm%)

Dog No.: 1112 Necropsy Date: 9 March 1976
 Dose Level (Mg/Day): 0 Day: 348

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)					γ
	Protein	Albumin	Globulin		$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	
-3	-	-	-	-	-	-	-	-	-
0	5.6	2.8	2.8	1.016	0.7	0.6	0.5	0.4	0.5
13	-	-	-	-	-	-	-	-	-
20	9.0	3.6	5.4	0.662	1.2	1.5	0.6	1.2	0.9
39	6.8	4.1	2.7	1.500	0.4	1.1	0.5	0.4	0.3
50	7.2	4.5	2.7	1.667	0.8	0.0	1.3	0.0	0.5

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Tissue HCB (PPM) Level at Necropsy

	Fat	
	Total	Lipid Extract
Bile		
	.024	0.33
		0.44

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URINALYSIS

ANIMAL NUMBER. (A/3-10) D1112F
 DAY ONE DATE 032875
 INITIAL BODY WEIGHT. 7.1 Kg
 FINAL BODY WEIGHT
 COMPOUND HCB
 DOSE Control
 ROUTE oral

Treatment Date	A(AU/11-16)	050275	062375	082075	121075	030476						
Day in Study	I(AU/17-19)	35	87	145	258	343						
Sp. Gr.	R(U1/20-24)	1.034	1.050	1.045	1.050	1.058						
pH	R(U1/25-29)	9	7	6	7.5	6						
Sugar	I(U1/30-34)	0	0	0	0	0						
Ketones	I(U1/35-39)	0	0	0	0	0						
Blood	I(U1/40-44)	0	0	0	0	0						
Protein	I(U1/45-49)	trace	trace	trace	trace	1+						
REAGENT STRIP												
MICROSCOPIC												
Triple Phosphates	I(U2/20-24)	4+	1+	2+								
Uric Acid	I(U2/25-29)											
Calcium Salts	I(U2/30-34)											
Other	A(U2/35-39)				2+ amorph	1+ amorph						
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	0	waxy								
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-3	0	0	0	0-1						
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-1	0	0-2	0-1	0-1						
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	*	0-4	0-1	0-1	2-4						
Mucous	I(U2/60-69)											
Appearance	I(U2/70-80)	yellow	yellow	yellow	cl	dk y						

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1112F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/9/76</u>
COMPOUND	<u>HC8</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>2:05 PM</u>
PATHOLOGY NUMBER	<u>76-1688</u>	DATE KILLED	<u>3/9/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>344</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01113
 SPECIES: DOG
 SEX: MALE
 AGE(MC): 9
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 LOT: 938872
 DAILY DOSE (MG/KG): 0.000000
 (MG/DOG): 0.000000
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/17	3/28	5/02	5/28	6/20	8/19	12/10	3/04
DAY:	11-	0	35	61	84	144	257	342
--HEMATOLOGY--								
HCT(Z)	42	44	46		50	49	58	53
HGB(GZ)	15.6	15.3	16.7		17.1	17.4	19.2	18.3
RBC(10 ¹⁶ /CMH)	5.99	6.03	4.99		6.58	6.73	7.51	7.44
WBC(10 ¹³ /CMH)	14.74	12.63	4.46		11.73	16.24	9.04	7.64
NEUT,I(ZWBC)	0.0	0.0	1.0		1.0	0.0	3.0	0.0
NEUT,M(ZWBC)	55.0	59.0	66.0		52.0	69.0	61.0	77.0
NEUT,N(10 ¹³)	8.11	7.45	2.94		6.10	11.21	5.51	5.88
LYMPHO(ZWBC)	29.0	19.0	29.0		35.0	25.0	28.0	22.0
LYMPHO(10 ¹³)	4.27	2.40	1.29		4.11	4.06	2.53	1.68
MONO(ZWBC)	4.0	5.0	1.0		5.0	2.0	0.0	1.0
EOSINO(ZWBC)	12.0	17.0	3.0		7.0	4.0	8.0	0.0
BASO(ZWBC)	0.0	0.0	0.0		0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0		0.0	0.0	0.0	0.0
RET(ZRBC)	0.4	0.4	0.7		0.4	0.7	0.1	0.0
THR(10 ¹⁴ /CMH)	24	36	21		20	17	20	26
PROTIME(SEC)	6.9	7.4	6.0		9.4	7.9	6.9	7.9

--BLOOD CHEM--

BUN(MGX)	15.8	18.1	18.5		16.5	16.9	16.8	15.5
BS(MGX)	77	80	80	76	71	67	80	76
AP(KAU)	6.4	5.0	3.6		3.9	4.3	3.0	3.6
SGOT(RFU/ML)	19	12	15		17	13	19	17
SGPT(RFU/ML)	15	14	14		14	13	15	15
BILI(MGX)								
CL-(MEQ/L)	115	112	113		114	113	120	117
CA++(MGZ)	10.7	10.6	10.0		9.6	11.6	10.6	10.2
PCO2(MEQ/L)	23.2	25.8	24.8		23.8	22.0	29.5	22.8
PH	7.347	7.390	7.400		7.362	7.220	7.492	7.306
PROTEIN(GZ)	5.80	6.00						6.00
PCO2(MMHG)	41.5	41.4	38.7		40.5	51.9	36.8	44.1

Serum Electrophoresis

(All Values = gm%)

Dog No.: 1113

Necropsy Date: 9 March 1976

Dose Level (Mg/Day): 0

Day: 344

Sampling Time (Weeks)	Total			Albumin/Globulin (Ratio)	α -1	α -2	β -1	β -2	γ
	Protein	Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	6.0	3.0	3.0	1.000	0.5	0.9	0.7	0.6	0.4
13	-	-	-	-	-	-	-	-	-
20	8.4	3.6	4.8	0.738	0.9	1.5	0.7	0.7	1.0
39	6.5	4.9	1.6	3.107	0.7	0.0	0.7	0.0	0.2
50	6.5	3.6	2.9	1.250	0.5	0.8	0.9	0.5	0.2

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Tissue HCB (PPM) Level at Necropsy

Bile	Fat	
	Total	Lipid Extract
.059	0.86	1.38

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1113M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/9/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>3:30 PM</u>
PATHOLOGY NUMBER	<u>76-1689</u>	DATE KILLED	<u>3/9/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>344</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01122
 SPECIES: DOG
 SEX: FEMALE
 AGE(MO): 8
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT: HCB
 DRUG: LOT : 938872
 DAILY DOSE (MG/KG) :
 (MG/DOG) :
 SCHEDULE : DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL
 FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE: 3/18 3/28 5/02 6/20 8/19 12/10 3/04
 DAY: 10- 0 35 84 144 257 342

--HEMATOLOGY--

HCT(%)	46	45	53	50	50	55	44
HGB(GZ)	16.5	15.9	17.7	18.1	16.5	19.0	16.1
RBC(10 ¹⁶ /CMM)	6.54	6.44	5.53	6.60	6.77	7.64	6.73
WBC(10 ¹³ /CMM)	10.16	8.08	3.37	12.63	8.69	8.24	8.32
NEUT,I(ZWBC)	0.0	0.0	1.0	2.0	1.0	2.0	0.0
NEUT,M(ZWBC)	48.0	48.0	53.0	60.0	59.0	54.0	59.0
NEUT,M(10 ¹³)	4.88	3.88	1.79	7.58	5.13	4.45	4.91
LYMPHO(ZWBC)	42.0	43.0	33.0	25.0	36.0	33.0	40.0
LYMPHO(10 ¹³)	4.27	3.47	1.11	3.16	3.13	2.72	3.33
MONO(ZWBC)	2.0	3.0	3.0	8.0	0.0	5.0	1.0
EOSINO(ZWBC)	8.0	6.0	10.0	5.0	4.0	6.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	1.3	0.6	0.5	0.7	1.1	0.6	0.0
THR(10 ¹⁴ /CMM)	27	27	25	18	26	17	25
PROTIME(SEC)	8.0	8.4	6.0	7.9	7.0	6.9	7.4

--BLOOD CHEM--

BUN(MGZ)	16.1	21.5	17.1	24.4	17.9	20.2	21.6
BS(MGZ)	90	88	80	65	84	73	72
AP(KAU)	2.8	4.4	5.0	4.8	4.3	3.6	3.9
SGOT(RFU/ML)	15	13	14	13	14	12	11
SGPT(RFU/ML)	15	15	14	12	9	12	13
BILI(MGZ)							
CL-(MEQ/L)	111	113	111	113	113	115	117
CA++(MGZ)	10.2	11.0	10.4	10.2	11.2	10.6	11.0
PCO2(MEQ/L)	28.6	26.2	24.0	22.0	26.0	29.8	25.0
PH	7.275	7.360	7.401	7.330	7.380	7.466	7.373
PROTEIN(GZ)	6.10	6.10	37.4	40.7	43.1	40.5	6.90
PCO2(MMHG)	60.3	45.4					41.5

Serum Electrophoresis

(All Values = gm %)

Dog No.: 1122

Necropsy Date: 10 March 1976

Dose Level (Mg/Day): 0

Day: 349

Total

Sampling Time (Weeks)	Protein	Albumin	Globulin	Albumin/Globulin (Ratio)	<u>α-1</u>	<u>α-2</u>	<u>β-1</u>	<u>β-2</u>	<u>γ</u>
-3	-	-	-	-	-	-	-	-	-
0	6.1	3.4	2.7	1.278	0.6	0.5	0.5	0.4	0.5
13	-	-	-	-	-	-	-	-	-
20	8.5	3.2	5.3	0.616	0.9	1.5	0.5	1.3	1.1
39	7.1	4.7	2.4	1.973	1.0	0.4	0.8	0.0	0.2
50	7.7	4.4	3.3	1.339	1.1	0.8	1.1	0.0	0.3

Tissue HCB (PPM) Level at Necropsy

<u>Fat</u>	
<u>Total</u>	<u>Lipid Extract</u>
0.52	0.69

<u>Bile</u>
.029

URINALYSIS

ANIMAL NUMBER	(A/3-10)	D1122F	COMPOUND	HCB
DAY ONE DATE		032875	DOSE	Control
INITIAL BODY WEIGHT		7.6 Kg	ROUTE	oral
FINAL BODY WEIGHT				

Treatment Date	A(UA/11-16)	050275	5062375	582075	121075	030476
Day in Study	I(AU/17-19)	35	87	145	258	343
Sp. Gr.	R(U1/20-24)	1.040	1.040	1.050	1.056	1.070
pH	R(U1/25-29)	9	6	6	6	5.5
Sugar	I(U1/30-34)	0	0	0	0	0
Ketones	I(U1/35-39)	0	0	0	0	1+
Blood	I(U1/40-44)	0	mod.	0	0	0
Protein	I(U1/45-49)	3+	trace	trace	1+	1+

MICROSCOPIC						
Triple Phosphates	I(U2/20-24)					
Uric Acid	I(U2/25-29)	1+				
Calcium Salts	I(U2/30-34)			2+		
Other	A(U2/35-39)					
Casts/LPF 100X (Avg/Field)	I(U2/40-44)	0	waxy	waxy		
RBC/HPF 400X (Avg/Field)	I(U2/45-49)	0-1	0	0	2-3	2-3
WBC/HPF 400X (Avg/Field)	I(U2/50-54)	0-1	0	1-5	20-30	0-1
EPITH/HPF 400X (Avg/Field)	I(U2/55-59)	0-3	5-10	0-2	1-2	1-2
Mucous	I(U2/60-69)					
Appearance	I(U2/70-90)	yellow	yellow	yellow	yellow	dk cly

*** Too numerous to count**

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1122F</u>	SEX	<u>Female</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/10/76</u>
COMPOUND	<u>HCb</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>2:30 PM</u>
PATHOLOGY NUMBER	<u>76-1742</u>	DATE KILLED	<u>3/10/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>345</u>

SUMMARY:

DRUG INDUCED LESIONS

None

ANIMAL ID: D01129
 SPECIES: DOG
 SEX: MALE
 AGE(MO): 8
 RX-DATE: 3/28/75
 SUPPLIER: MARSHALL

TREATMENT:
 DRUG: HCB
 LOT: 938872
 DAILY DOSE (MG/KG):
 (MG/DOG):
 SCHEDULE: DAILY FOR TWELVE MONTHS

ROUTE OF ADMIN: ORAL

FORMULATION
 VEHICLE: LACTOSE
 CONCENT(MG/ML):

NO GRADES

DATE:	3/18	3/28	5/02	6/20	8/19	12/10	3/04
DAY:	10-	0	35	84	144	257	342
--HEMATOLOGY--							
HCT(Z)	38	41	43	45	44	46	42
HGB(GZ)	13.9	15.0	15.2	16.2	16.0	16.3	16.6
RBC(10 ¹⁶ /CMM)	5.81	6.10	4.39	6.51	6.73	7.07	6.95
WBC(10 ¹³ /CMM)	11.50	11.18	2.89	14.51	9.31	6.19	9.73
NEUT,I(ZWBC)	0.0	0.0	2.0	3.0	0.0	2.0	0.0
NEUT,M(ZWBC)	46.0	58.0	58.0	42.0	62.0	64.0	80.0
NEUT,M(10 ¹³)	5.29	6.48	1.68	6.09	5.77	3.96	7.78
LYMPHO(ZWBC)	49.0	32.0	31.0	45.0	34.0	34.0	20.0
LYMPHO(10 ¹³)	5.64	3.58	0.90	6.53	3.17	2.10	1.95
MONO(ZWBC)	2.0	1.0	2.0	3.0	0.0	0.0	0.0
EOSINO(ZWBC)	3.0	9.0	7.0	7.0	4.0	0.0	0.0
BASO(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
NORMBL(ZWBC)	0.0	0.0	0.0	0.0	0.0	0.0	0.0
RET(ZRBC)	0.9	0.6	1.0	1.1	2.2	0.5	0.0
THR(10 ¹⁴ /CMM)	23	25	26	18	23	21	39
PROTIME(SEC)	8.4	7.9	7.0	8.4	7.0	6.4	7.4

--BLOOD CHEM--

BUN(MGZ)	16.1	18.9	17.3	20.8	20.8	20.7	16.9
BS(MGZ)	93	100	82	72	68	80	80
AP(KAU)	3.0	3.6	5.1	3.6	2.1	2.0	1.6
SGOT(RFU/ML)	14	15	16	18	12	15	14
SGPT(RFU/ML)	16	18	16	15	12	18	15
BILI(MGZ)	117	112	118	115	112	115	120
CL-(MEQ/L)	10.8	10.6	10.4	9.8	11.2	10.0	11.0
CA++(MGZ)	25.8	24.5	23.8	23.0	24.0	29.8	24.0
PCO2(MEQ/L)	7.300	7.385	7.376	7.350	7.370	7.499	7.360
PH	6.10	5.90					6.20
PROTEIN(GZ)	51.0	40.1	39.2	40.0	40.1	37.4	41.3
PCO2(MMHG)							

Serum Electrophoresis

(All Values = gm%)

Necropsy Date: 10 March 1976
Day: 349

Dog No.: 1129
Dose Level (Mg/Day): 0

Sampling Time (Weeks)	Protein	Total		Albumin/Globulin (Ratio)	$\alpha-1$	$\alpha-2$	$\beta-1$	$\beta-2$	γ
		Albumin	Globulin						
-3	-	-	-	-	-	-	-	-	-
0	5.9	3.5	2.4	1.500	0.3	0.4	0.6	0.6	0.5
13	-	-	-	-	-	-	-	-	-
20	8.7	3.0	5.7	0.523	1.4	1.8	0.6	1.1	0.8
39	6.6	5.2	1.4	3.700	0.5	0.0	0.3	0.4	0.3
50	6.4	4.4	2.0	2.226	0.3	0.4	1.1	0.0	0.1

Tissue HCB (PPM) Level at Necropsy

Fat	
Total	Lipid Extract
1.03	1.75

Bile
0.06

Page

URINALYSIS

ANIMAL NUMBER. (A/3-10) D1129M
DAY ONE DATE 032875
INITIAL BODY WEIGHT. 10.5 Kg
FINAL BODY WEIGHT

COMPOUND HCB
DOSE Control
ROUTE oral

Treatment Date	AIAU/11-16)	050275062375	082075	121075	030476				
Day in Study	IIAU/17-19)	35	87	145	258	343			
Sp. Gr.	RI(U1/20-24)	1.033	1.065	1.055	1.064	1.050			
pH	RI(U1/25-29)	9	6	6	6	6			
Sugar	RI(U1/30-34)	0	0	0	0	0			
Ketones	RI(U1/35-39)	0	0	0	0	0			
Blood	RI(U1/40-44)	0	0	0	0	0			
Protein	RI(U1/45-49)	trace	1+	trace	1+	1+			
REAGENT STRIP									
MICROSCOPIC									
Triple Phosphates	II(U2/20-24)	2+			1+	2+			
Uric Acid	II(U2/25-29)			2+					
Calcium Salts	II(U2/30-34)								
Other	AI(U2/35-39)		sperm		sperm	sperm			
Casts/LPF 100X (Avg/Field)	II(U2/40-44)	0	0	waxy	0	2-3			
RBC/HPF 400X (Avg/Field)	II(U2/45-49)	0	0	0	0	2-3			
WBC/HPF 400X (Avg/Field)	II(U2/50-54)	0-2	0	5-10	40-70	1-2			
EPITH/HPF 400X (Avg/Field)	II(U2/55-59)	0-3	5-10	*		4-5			
Mucous	II(U2/60-69)								
Appearance	II(U2/70-80)	yellow	dk. y	yellow	yellow	cl dk y			

* Too numerous to count

NECROPSY AND PATHOLOGY REPORT

ANIMAL NUMBER	<u>D1129M</u>	SEX	<u>Male</u>
DAY ONE DATE	<u>3/28/75</u>	NECROPSY DATE	<u>3/10/76</u>
COMPOUND	<u>HCB</u>	EUTHANIZED WITH	<u>Na pentobarbital</u>
DOSE Mg/Da	<u>Control</u>	HOUR DIED	<u>9:45 AM</u>
PATHOLOGY NUMBER	<u>76-1741</u>	DATE KILLED	<u>3/10/76</u>
SPECIES	<u>Beagle dog</u>	PRENECROPSY CONDITION	<u>Excellent</u>
AGE	<u>21 mo</u>	POSTMORTEM STATE	<u>Excellent</u>
NUMBER OF TREATMENTS AND DAY OF NECROPSY			<u>345</u>

SUMMARY:

DRUG INDUCED LESIONS

None